DISSERTATION

on

SERUM CREATINE KINASE AND MAGNESIUM AS PROGNOSTIC INDICATORS IN ACUTE ORGANOPHOSPHORUS POISONING

submitted in partial fulfillment of requirements for

MD DEGREE EXAMINATION

BRANCH-I GENERAL MEDICINE

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI

INSTITUTE OF INTERNAL MEDICINE

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CHENNAI – 600003

APRIL 2013

CERTIFICATE

This is to certify that the dissertation titled **"SERUM CREATINE KINASE AND MAGNESIUM AS PROGNOSTIC INDICATORS IN ACUTE ORGANOPHOSPHORUS POISONING"** is a bona fide work done by **Dr. R. SUBRAMANIAN**, Post Graduate student, Institute of Internal Medicine, Madras Medical College, Chennai – 600003, in partial fulfillment of the university rules and regulations for the award of MD DEGREE in GENERAL MEDICINE BRANCH-I, under our guidance and supervision, during the academic period from April 2010 to April 2013.

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DECLARATION

I solemnly declare that the dissertation titled **"SERUM CREATINE KINASE AND MAGNESIUM AS PROGNOSTIC INDICATORS IN ACUTE ORGANOPHOSPHORUS POISONING"** was done by me at Madras Medical College, Chennai – 600003, during the period June 2012 to November 2012 under the guidance and supervision of Prof. N. RAGHU, MD, to be submitted to The Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of requirements for the award of MD DEGREE in GENERAL MEDICINE BRANCH-I.

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ACKNOWLEDGEMENT

I thank **Prof. V. KANAGASABAI, MD**, Dean, Madras Medical College, for having permitted me to conduct the study and use the hospital resources in the study.

I express my heartfelt gratitude to **Prof. N. RAGHU, MD**, Director, Institute of Internal Medicine, for his inspiration, advice and guidance in making this work complete.

I am extremely thankful to **Dr. M. ANUSUYA, MD**, Assistant Professor, Institute of Internal Medicine and **Dr. D.K. SIVAKUMAR, MD**, Assistant Professor, Institute of Internal Medicine, for guiding me academically and professionally during the period of study.

I also thank all the postgraduate students and paramedical staff for their cooperation which enormously helped me in the study. I am also indebted to thank all the patients and their caring relatives. Without their humble cooperation, this study would not have been possible.

ABBREVIATIONS

CK	creatine kinase
Mg	magnesium
OPC	organophosphate compounds
Ach	acetyl choline
AchE	acetylcholinesterase
Ch	choline
ODIDP	organophosphate induced delayed polyneuropathy
COPIND	chronic organophosphate induced neuropsychiatric disorder
POP	Paradeniya organophosphorus poisoning
SGOT	serum glutamate oxaloacetate transaminase
LDH	lactate dehydrogenase
mg	milligram
IU	international units
dl	deciliter
gm	gram
P2AM	pralidoxime

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INTRODUCTION

Agriculture constitutes the major component of Indian economy. Pesticides are wonderful human inventions used for the control of pests, weeds or plant diseases to improve the cultivation of agricultural products. It also had been used as chemical warfare weapons.

In India, agriculture is still labour-intensive. So, man is exposed to such chemicals at all stages of pesticide formulation, manufacturing and spraying in his farm. Pesticides has got both acute and chronic health hazards upon exposure either by occupational or by self- harm(1).

Poisoning constitutes about 60% of self-harm(1) in rural Asia. Organophosphate compounds account for 80% of pesticide poisoning. Ravi et al described the incidence of organophosphorus poisoning as around 1.26 lakhs during the year 2007 in India. In our poison centre, Rajiv Gandhi Government General Hospital, Chennai, 330 and 244 cases of acute organophosphorus poisoning admitted respectively in 2010 and 2011 with a mortality rate of 19% mostly due to respiratory paralysis and mechanical ventilation related complications.

Even with this background, the medical management of acute organophosphorus poisoning is deficient in evidence based management protocols and research tool. This calls for our urgent comprehensive analysis of acute organophosphorus poisoning which may be helpful in renovating the protocol in its management to reduce mortality.

OBJECTIVES

1. To assess and categorize the severity of organophosphorus poisoning cases clinically, on admission by Peradeniya Organophosphorus Poisoning scale.

2. To estimate the serum levels of creatine kinase and magnesium on admission in acute organophosphorus poisoning.

3. To correlate the serum levels of creatine kinase and magnesium with the clinical severity scoring.

4. To correlate the serum levels of creatine kinase and magnesium with the atropine requirement during the course in hospital.

5. To correlate the serum levels of creatine kinase and magnesium with one or more of complications like respiratory paralysis, intermediate syndrome and the need for mechanical ventilation, acute renal failure, seizures, arrhythmias and coma.

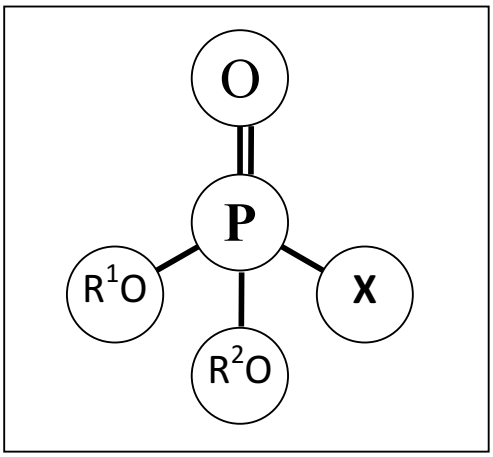
REVIEW OF LITERATURE

Historical Background

Organophosphorus compounds are a diverse group of chemicals used as pesticides. They have been first synthesized by Lassaigne during early 1800s on observing the reaction of alcohol with phosphoric acid. In 1854, Clermont(2) prepared Tetro Ethyl Pyrophosphate (TEPP). Lange succeeded in the synthesis of dimethyl diethyl phosphor fluoridates in 1932. Lange in Berlin investigated the use of these chemicals as pesticides, but German military(3) used it as chemical warfare agents (i.e. tabun, sarin, soman). In 1941, during World War II, the organophosphates were reintroduced as insecticides as originally intended. Jamaican Jinger Palsy incident in 1930, due to suicidal and accidental exposure to organophosphate compounds led to probe into its mechanism of action. In 1944, Schrader, synthesized parathion and was widely used as insecticides. In 1955, Davies introduced oximes and its usefulness in organophosphorus poisoning. Mass poisoning happened in 2005, following ethion contaminated food in India.

General Chemical Structure

Organophosphorus compounds are basically the esters of phosphoric acid in which a terminal oxygen is connected to phosphorus by a double bond, whereas two lipophilic groups and a leaving group is connected to phosphorus by a single bond.



R – denotes either ethyl or methyl group

X – denotes leaving group

Leaving group is the principal metabolite for species identification.

PHARMACOKINETICS

Organophosphates can be absorbed percutaneously and also when ingested, inhaled or injected. The kinetics depend upon many factors such as:

1. Route of administration
2. Distance from target organs
3. Local vs systemic metabolism and activation
4. Route of elimination
5. Endogenous hydrolysis by non-specific esterases.

The chemicals are equally distributed in all tissues but predominantly in liver and kidneys. Plasma half life ranges from few minutes to few hours depending upon the type of compounds and route of exposure. Metabolism occurs either by oxidation, hydrolysis by esterases or by transfer of portion of molecule to glutathione. 80 – 90% of compound is eliminated within 48 hours of exposure by urinary and fecal excretion. Most of agents show symptoms and signs within six to ten hours of exposure with the exception of fat soluble compounds where it may take several days to weeks to manifest because the substance may be leached out of the fat.

CLASSIFICATION OF ORGANOPHOSPHORUS COMPOUNDS(4)

A.HIGHLY TOXIC

Monochrotophos

Phosphamindon

Ethyl Parathion

Chlorthiophos

Dichlorovas

Methyl Parathion

B.MODERATELY TOXIC

Malathion

Chlorpyrifos

Temephos

Diazinon

Fenthion

C.LEAST TOXIC

Triazophos

Parathion

Quinalphos

Dimethoate

Prophenophos

Figure 1: Organophosphorus compounds commonly encountered in our poison center

MECHANISM OF ACTION

Acetylcholine (Ach) is the neurotransmitter in central and peripheral nervous system at all postganglionic parasymphathetic nerve endings, at synapses of both sympathetic and parasympathetic ganglia and also at skeletal muscle myoneural junction. Acetyl cholinesterase (AchE) is an enzyme localized in central nervous system in various organs and glands which hydrolyses acetylcholine into acetic acid and choline (Ch).

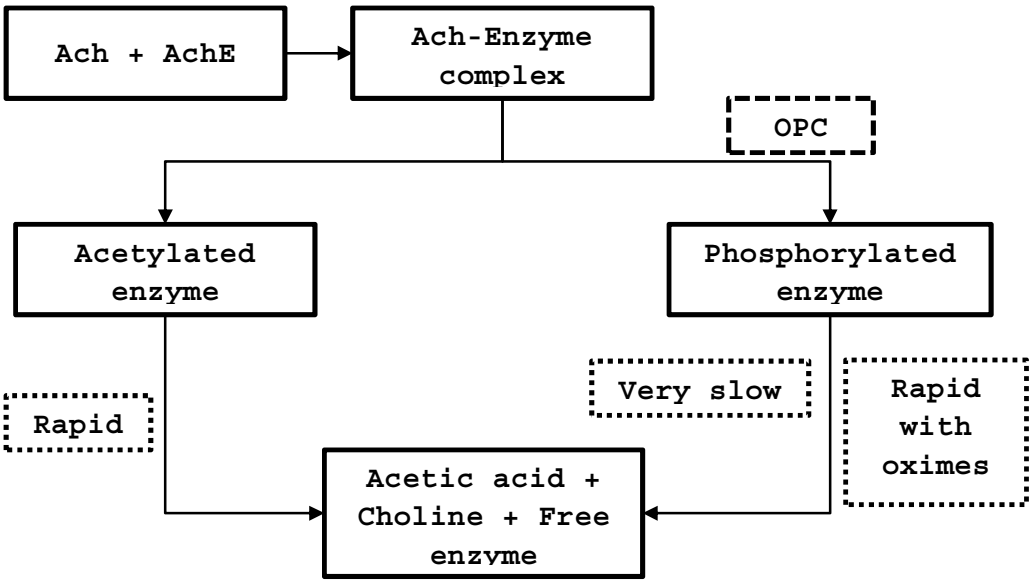
AchE is present in two forms.

1. True acetyl cholinesterase – found in tissues and erythrocytes
2. Pseudocholinesterase – found in serum and liver.

Organophosphates are the acid transferring inhibitors of cholinesterase by phosphorylation of the enzyme. The reactivation of enzyme may occur spontaneously or may be enhanced by oximes.

Acetylcholine binds with acetylcholinesterase enzyme and forms acetylcholine-enzyme complex. Subsequently the enzyme gets acetylated. The acetylated enzyme undergoes hydrolysis and forms acetic acid and choline releasing the free enzyme. This physiological reaction is a rapid one.

In the presence of organophosphorus compounds, the acetylcholine-enzyme complex becomes phosphorylated instead of getting acetylated. Once the enzyme becomes phosphorylated, its conversion to free enzyme is a very slow process. Non-availability of free enzyme leads to excess acetylcholine in the synapse and neuromuscular junction leading onto the toxic clinical consequences. Oximes accelerate the conversion of phosphorylated enzyme to free enzyme.



CLINICAL FEATURES

Symptoms and signs of organophosphorus poisoning:

Muscarinic manifestations

GASTRO-INTESTINAL

- Nausea / vomiting
- Increased salivation
- Diarrhoea

CARDIO-VASCULAR

- Hypotension
- Bradycardia
- Arrythmias

RESPIRATORY

- Rhinorrhea
- Bronchorrhea
- Bronchospasm

GENITO URINARY

- Urinary incontinence

EYES

- Diplopia
- Lacrimation

- Miosis

GLANDS

- Salivation
- Sweating

Nicotinic manifestations

MUSCULO-SKELETAL(5)

- Weakness
- Fasciculation
- Cramps
- Paralysis

CARDIO-VASCULAR

- Hypertension
- Tachycardia
- Arrythmias

Central manifestations

- Anxiety
- Ataxia
- Convulsions

- ❖ Insomnia
- ❖ Tremors
- ❖ Dysarthria
- ❖ Coma
- ❖ Absent reflexes
- ❖ Respiratory depression

The manifestations of toxic features of organophosphorus compounds depend on the agent, quantity, route of entry, rate and amount of systemic absorption and are usually seen within 30 minutes to 3 hours.

Gastrointestinal manifestations:

Symptoms of vomiting, diarrhoea and abdominal cramps are first to occur after oral ingestion.

Respiratory manifestations:

The integrity of airway will be compromised by excessive secretions. Paralysis of both respiratory and oropharyngeal muscles occur due to nicotinic effects leading on to airway obstruction and aspiration of gastric contents. Central nervous system depression leads to respiratory arrest.

Cardiac manifestations(6):

They are often the cause for serious complications and fatality. Mechanisms may be due to direct toxicity on the myocardium or due to other contributory factors like hemodynamic alteration, acidosis, hypoxia, electrolyte abnormalities and high dose atropine therapy.

Neurological manifestations:

It has been the primary focus of interest which may necessitate prolonged mechanical ventilation due to neuromuscular weakness.

Type I paralysis or acute cholinergic crisis:

It is seen in initial phase of exposure characterized by muscle fasciculation, weakness, cramps, may require ventilator support. This phase usually passes off within 48 – 72 hours. Muscle fiber necrosis have been described in this phase and leads to increased serum levels of muscle enzymes(7).

Type II paralysis or Intermediate syndrome(8):

It usually develops 12 – 96 hours of exposure. The proposed mechanisms for development of intermediate syndrome are:

a. Different susceptibility of various cholinergic receptors
b. Muscle necrosis
c. Prolonged AchE inhibition

d. Inadequate oxime therapy

e. Oxidative stress related myopathy

This phase is characterized by weakness of neck flexors, respiratory muscles, proximal limb muscles and motor cranial nerves like III, IV and VI with sparing of distal muscle groups. This phase persists for 4 – 18 days and may require mechanical ventilation.

Type III paralysis or organophosphate induced delayed polyneuropathy (OPIDP)(9)

This type of distal motor axonopathy follows after a period of 7 – 21 days of exposure which is usually manifested by weakness of small muscles of hands and foot drop with sparing of cranial nerves and autonomic nervous system. Deep tendon reflexes will be absent. Severe manifestations will be left with persistent deficits.

Chronic Organophosphate induced neuropsychiatric disorder (COPIND)(10)

These are the long term effects following the acute exposure to high dose of organophosphorus compounds. The manifestations are anxiety, depression, memory disturbances, schizophrenia, dystonic reactions,cog-wheel rigidity. The cause could be attributed to the sequelae of cardiac arrhythmias, convulsions, respiratory failure and anoxia.

Immunological alterations:

Severe cholinergic stimulation may suppress the immune system either directly by acetylcholine or indirectly by the metabolic products of organophosphorus compounds. There may be a decrease in neutrophil chemotaxis. It will lead onto autoimmune reactions and suppresses the antibody response to vaccines. The individuals are more prone for frequent viral infections in long term.

Endocrine manifestations:

There may be increased release of hormones such as Adrenocorticotrophic hormone (ACTH), Prolactin and Vasopressin due to effect on nicotinic receptors in brain. Non-ketotic hyperglycemia, glycosuria and reduced thyroxin production are other consequences.

CLINICAL SEVERITY SCORING:

The following are the grading of clinical severity useful in organophosphorus poisoning.

1. Poisoning Severity Scale (PSS)
2. Modified Dreisbach Clinical Criteria
3. Peradeniya Organophosphorus Poisoning scale

The Peradeniya Organophosphorus Poisoning scale(7):

Parameters	Criteria	Score
Pupil size	≥2mm	0
	<2mm	1
	Pin point	2
Respiratory rate	<20/min	0
	≥20/min	1
	≥20/min with central cyanosis	2
Heart rate	>60/min	0
	41 – 60/min	1
	<40/min	2
Fasciculation	None	0
	Present, generalized / continuous	1
	Both generalized and continuous	2
Level of consciousness	Conscious and rationale	0
	Impaired response to verbal commands	1
	No response to verbal commands	2
Seizures	Absent	0
	Present	1

Note : 0 – 3 Mild Poisoning; 4 – 7 moderate poisoning; 8 – 11 severe poisoning

DIAGNOSTIC MODALITIES

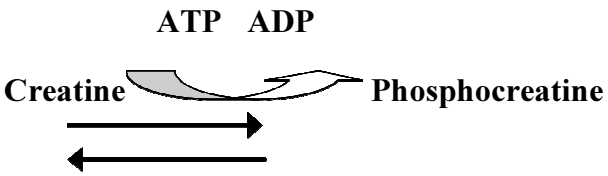
I. Enzyme Levels:

i. Cholinesterase:

The diagnosis of organophosphorus poisoning may be confirmed by the reduction of RBC cholinesterase activity(11), expressed as percentage, for which results won't be readily available. Hence, RBC cholinesterase level is a useful marker which correlates better with CNS acetylcholine levels than plasma cholinesterase. It may show false positive results due to its depressed levels seen in pernicious anemia, hemoglobinopathies and with the use of antimalarial drugs. Plasma cholinesterase levels below 5000 IU/L can be taken as the corroborative evidence of organophosphorus poisoning. Since it is an acute phase reactant produced in liver, it can be increased during pregnancy and infections. Its level may be low in liver dysfunction, low protein conditions, use of drugs like succinylcholine, codeine, morphine, etc.,

ii. <u>Creatine kinase:</u>

Creatine kinase(12) is the enzyme expressed by various tissues like skeletal muscles, heart, brain, retina, hair cells of inner ear and smooth muscles. It catalyses the conversion of creatine to phosphocreatine by consuming ATP to form ADP.



They exist as two forms.

1. Mitochondrial CK enzyme
2. Cytosolic CK → 3 isoenzymes

CK-MM → Skeletal muscles

CK-MB → Heart

CK-BB → Brain

Normal levels of creatine kinase in serum is between 60 -400 IU/L. In acute organophosphorus poisoning, serum CK level is elevated both in acute cholinergic phase and intermediate syndrome due to muscle fiber necrosis.

Other conditions causing elevated serum CK are chronic alcohol abuse, myopathies, chronic liver disease, malignancy, renal failure, seizure, myocardial infarction, drugs like statins, steroids, etc.,

iii. Other enzymes:

SGOT, LDH, amylase, lipase may be elevated .

II. Gastric aspirate and blood analysis – for estimation of organophosphate compounds.

III. Renal Function Test:

- ❖ Elevated serum creatinine and BUN
- ❖ Hypokalemia
- ❖ Hyperkalemia

IV. Complete Blood count – Leukocytosis and hemoconcentration due to fluid loss.

V. Arterial Blood Gas analysis - Metabolic acidosis, hypoxia, hypercapnia

VI. Chest X Ray – Aspiration pneumonitis, pulmonary edema

VII. Electrocardiogram – Prolonged Q-T interval, S-T segment elevation, prolonged P-R interval, sinus brady/tachycardia, ventricular tachycardia, ventricular fibrillation.

There are three phases of cardiotoxicity described by Ludomirsky et al.

Phase I - A brief period of increased sympathetic tone

Phase II - Prolonged period of parasympathetic tone with A-V blockade

Phase III - QT prolongation, Torsades de pointes(TdP), ventricular Tachycardia / fibrillation.

VIII. Nerve Conduction Study(13) :

- ❖ Repetitive firing from single stimulus
- ❖ Decremental – incremental response
- ❖ Decremental response

IX. Serum Magnesium

Acute Organophosphorus poisoning will produce hypomagnesemia(14) due to:

- ❖ Prolonged nasogastric suction
- ❖ Severe diarrhea
- ❖ Underlying illness like starvation, chronic alcoholism, diabetes, hyperthyroidism, chronic kidney disease.
- ❖ Normal plasma magnesium concentration is 1.7 – 2.1 mg/dl.

Magnesium is involved in metabolism of proteins, fats and carbohydrates and act as cofactor for the enzyme ATPase.

Extracellularly, magnesium ion interferes with the release of acetylcholine and blocks neurosynaptic transmission. Hypokalemia is usually associates with hypomagnesemia.

Manifestations of hypomagnesemia

CARDIAC	NEUROMUSCULAR
❖ Arrythmias – Atrial/Ventricular ❖ Hypertension	❖ Convulsions ❖ Muscle cramps ❖ Depression ❖ Generalised weakness ❖ Acute organic brain syndrome

Since the features of hypomagnesemia may be masked by organophosphorus toxic manifestations, its serum level may predict the outcome of patients with acute organophosphorus poisoning.

Studies relating to serum creatine kinase and magnesium levels to the severity of acute organophosphorus poisoning

1. A study conducted at Kolkata Medical College, India by Kuntal Bhattacharyya et al, employing 63 patients of acute organophosphorus poisoning found the correlation between initial increased serum creatine kinase levels and increased risk for complications like respiratory paraysis, arrhythmias, increased atropine requirement, acute kidney injury, etc.,
2. Vanneste Y et al proved the biochemical monitoring of rhabdomyonecrosis in organophosphorus poisoning by serum acetylcholinesterase and creatine kinase levels.
3. Dursum Aygun et al studied employing 47 patients with acute organophosphorus poisoning and conducted that there was no difference in initial serum levels of creatine kinase and aspartate aminotransferase in patients with and without intermediate syndrome and it may not predict the subsequent development of intermediate syndrome.
4. Shubhakaran et al from Dr.S.N.Medical College, Jodhpur, Rajasthan have documented hypomagnesemia in many organophosphorus poisoning cases(16).

5. Bar-Meir et al proposed hypomagnesemia, hypokalemia or hypocalcemia may be the factors causing electrocardiographic features of QT prolongation and Torsades de pointes in acute organophosphorus poisoning.
6. Abdolkarim Pajoumand et al from Loghman-Hakim Hospital, Tehran, Iran concluded that the administration of MgSO4 intravenously along with other conventional therapies, will be beneficial in reducing the mortality rate(15).

No study yet conducted correlating the serum levels of magnesium with the severity of acute organophosphorus poisoning.

MANAGEMENT

General Care

- Check airway, breathing and circulation.
- Place the patient in left lateral position with head lower than the feet to prevent aspiration.
- Supplement high flow oxygen and intubate if warranted.
- Start infusion of Normal Saline to keep systolic blood pressure of more than 80 mmHg.

Skin decontamination

- Remove all the clothing and gently cleanse the patient with soap and water to prevent absorption(17).

Eye decontamination

- Irrigate the eyes with normal saline, if there is ocular exposure.

Gastric lavage

- Insert nasogastric tube and start lavage within an hour of ingestion using Normal Saline or clean tap water 200 – 300 ml each time without any dwelling period until vomitus becomes clear.

Activated charcoal

- Activated charcoal absorbs the poisoning material in gut and facilitates excretion by its absorbing and expandable property. Multidosing is usually necessary in dose of 1 gm/kg/dose, diluted in 150 ml of water with 30 mg of magnesium sulfate every 2 – 4 hrs for 24 – 48 hours given through Ryle's tube. It is contraindicated with ileus or with intestinal obstruction.

The clinical parameters to be monitored in ICU are:

- Pulse
- Blood Pressure
- Respiratory rate
- Temperature
- Urine output

- Electrocardiogram
- Fasciculation
- SPO2
- Pupillary size
- Lung signs

Atropine

Atropine is the antimuscarinic agent of choice started with the dose of 3 – 5 mg rapid intravenous bolus every 5 – 10 minutes till the development of signs of atropinisation like:

- **Dry axilla**
- **Heart rate >80/min**
- **Clear lungs**
- **No more pinpoint pupils**
- **Systolic BP >80mmHg**

Double the initial dose, if the parameters are not achieved, till adequate atropinisation.

Then, maintain atropinisation with 10 – 20% of bolus dose given as infusion in 100 ml of normal saline with assessment every 15 minutes. The dose of atropine should be tailored down hourly for the next 24 hours. Watch for atropine toxicity like agitation, confusion, urinary retention, ileus, hyperthermia and tachycardia.

PRALIDOXIME (P_2AM):

It helps to reactivate the acetylcholinesterase(18). It has three main actions.

1. A direct reaction converting the organophosphate to a harmless compound.
2. A transient reaction protecting the enzyme from further inhibition.

3. Reactivation of inhibited alkyl phosphorylated enzyme to free the active unit.

The dose is 30 mg/kg bolus followed by 8 mg/kg/hr for next 48 hours. Then, it should be given 1 – 2 gm IV tds for next 5 days, given as infusion over a period of one hour in 100 – 200 ml of Normal Saline.

Rapid infusion may cause neuromuscular blockade, diastolic hypertension, convulsions, etc.,

Its action is most marked at the nicotinic skeletal neuromuscular junction and does not reverse the muscarinic actions. It should be started as early as possible before the permanent binding of organophosphate to acetylcholinesterase.

Few recent trials have questioned the beneficial effects of P_2AM in organophosphorus poisoning management(19,20).

IV Magnesium Sulfate

There are few studies quoting the beneficial effects of intravenous magnesium sulfate in organophosphorus poisoning. The probable mechanisms are:

1. Blocks ligand gated calcium channels and reduce the release of acetylcholine from presynaptic terminals.
2. Ventricular membrane stabilization, preventing arrhythmias
3. Increased hydrolysis of some pesticides.

Thus, our study is useful in the sense, serum magnesium level may correlate with the beneficial effect of intravenous magnesium sulfate.

Sodium bicarbonate

Sodium bicarbonate will increase the blood pH and decrease the mortality as per various studies and their effect is independent of correction of acidosis.

Seizures

Controlled with benzodiazepines like diazepam 10 – 20 mg IV or Lorazepam 4 mg IV.

Atropine delirium

Treated with midazolam 0.1 mg/kg or diazepam 10 – 20 mg IV.

Mechanical ventilation

It may be warranted in respiratory muscle weakness or respiratory depression.

Therapies under Trial

Organophosphorus hydrolases(21)

Isolated from Pseudomonas species which clears organophosphates thus reducing the blood and tissue concentration.

- N.Methyl / D-Aspartate receptor antagonists
- Gancyclidine reduces neuronal death, improves electroencephalogram and clinical recovery.

Butrylcholinesterase replacement therapy(21)

This is favoured by administration of fresh frozen plasma and plasmaparesis which increases the level of enzymes in the blood and neutralize the organophosphorus compounds.

α-2 adrenergic receptor agonists

Clonidine inhibits release of acetylcholine from presynaptic terminals of neuromuscular junctions.

Extracorporeal clearance (21)

It will be effective for some non-fat soluble organophsphorus compounds.

PREVENTION AND EDUCATION

Improved regulations of availability of pesticides and modifications of packaging of pesticides may all help reduced the use of organophosphates as poison. Adequate information to the public, regular training of health care providers, better availability of drugs/facilities and the establishment of poison information centres will facilitate in reducing the morbidity and mortality related to organophosphorus poisoning.

Insecticides should be kept out of reach of children to prevent accidental poisoning. Proper protective precautions should be taken during agricultural spraying to prevent inhalation and accidental ingestion of substance.

Pesticide poisoning contributes more than fifty percent of cases in our toxicology ICU and carries the mortality of around 19% (case register 2010 – 11). Our thesis of serum creatine kinase and magnesium levels in organophosphorus poisoning will surely aim in making or correcting the protocol for treatment of acute organophosphorus poisoning and also in reducing the morbidity and mortality of the patients admitted.

MATERIALS AND METHODS

Setting:

This study was conducted in the poison centre, Institute of Internal Medicine, Rajiv Gandhi Government General Hospital , Chennai.It was a cross sectional prospective study done during the period from June 2012 to November 2012.

60 patients, admitted as a case of acute organophosphorus poisoning with exposure within 12 hours irrespective of route of exposure, age and sex were selected and subjected for study with the consent.

Exclusion Criteria

1. Patients with other pesticide poisoning (e.g.organocarbamates) have been excluded by history and clinical features.
2. Patients with mixed poisoning were excluded.
3. Patients who had taken compounds with alcohol have been excluded.
4. Patients with known medical illness such as chronic liver disease, myopathy, malignancy, renal failure, autoimmune diseases, seizure disorder, coronary artery disease were excluded.

5. Patients who were on chronic drug usage with statins, steroids, diuretics have been excluded.
6. Pregnant patients were excluded from the study.

The eligible patients were assessed clinically on admission by Peradeniya Organophosphorus Poisoning scales and categorized according to the severity. They were subjected to routine blood investigations like blood sugar, blood urea, serum creatinine, liver function test, serum acetylcholinesterase, ECG and ABG. They also have been subjected to estimation of serum creatine kinase and magnesium levels on admission.

Bio chemical markers and the methods employed

1. Cholinesterase : Kinetic Calorimetric method
2. Creatine kinase : NAC activated method (kinetic)
3. Magnesium : Chlorphosphonazo III

First, the clinical severity by POP scoring were correlated with initial serum creatine kinase and magnesium levels.

Patients had been treated with our usual protocol with atropine and pralidoxime along with the usual care of poisoned patients. Atropine chart, input output chart, pulse / blood pressure chart, RFT chart had been maintained. Cardiac and SPO2 monitoring also done. Mechanical ventilation was considered with indications. The clinical course in terms

of atropine dose requirement, duration of hospital stay and development of complications like mechanical ventilation, intermediate syndrome, arrhythmias, renal failure, seizure, coma were correlated with the initial serum creatine kinase and magnesium levels.

Statistical methods

Statistical analysis was done using SPSS software. The following statistical methods have been employed for analysis:

1. Chi-square test
2. Unpaired student t-test
3. Analysis of variance (ANOVA)

RESULTS

DESCRIPTION OF STUDY POPULATION

Table : 1 AGE & SEX DISTRIBUTION

Age group	Male	Female	Total	Percentage
≤20	3	8	11	18.3%
21 – 30	10	12	22	36.7%
31 – 40	8	8	16	26.7%
>40	8	3	11	18.3%
Total	29	31	60	100%

In our series, among 60 patients taken for study. 37% constitutes the age group between 21 – 30 years. The number of people between the age group of 21 – 40 accounts for 38 out of 60 cases, which forms the majority. Female population predominates with 52%.

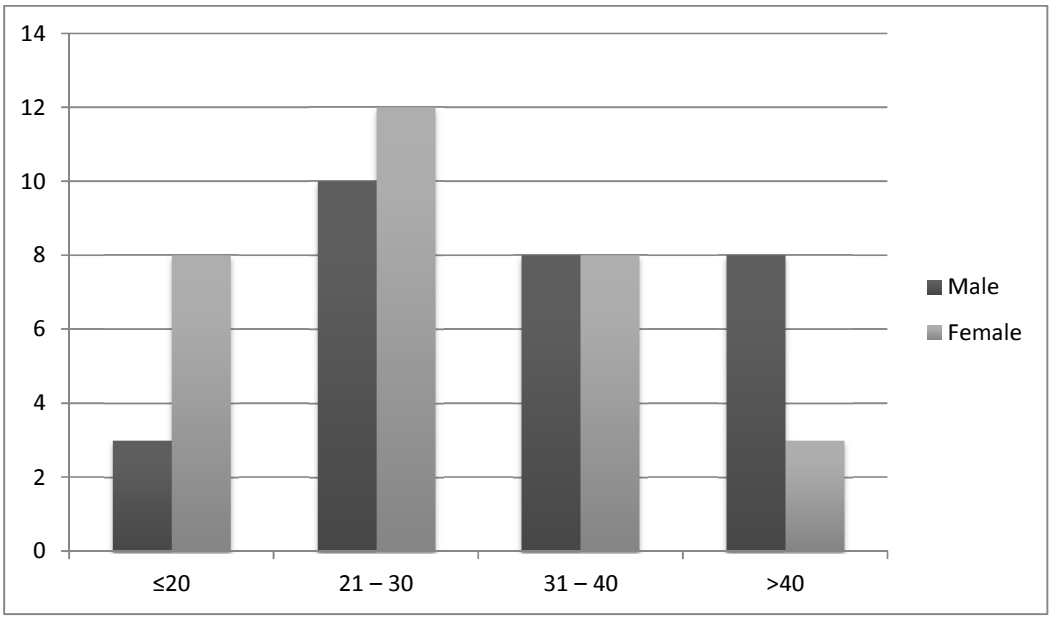


Table : 2 OCCUPATION

	Male	Female	Frequency (n)	Percentage
AGRICULTURE	**19**	**4**	**23**	**38%**
NON-AGRICULTURE	**10**	**27**	**37**	**62%**

Agriculturists make only 38% in our study population. Male patients dominate in agriculture and female patients dominate in non-agriculture as occupation.

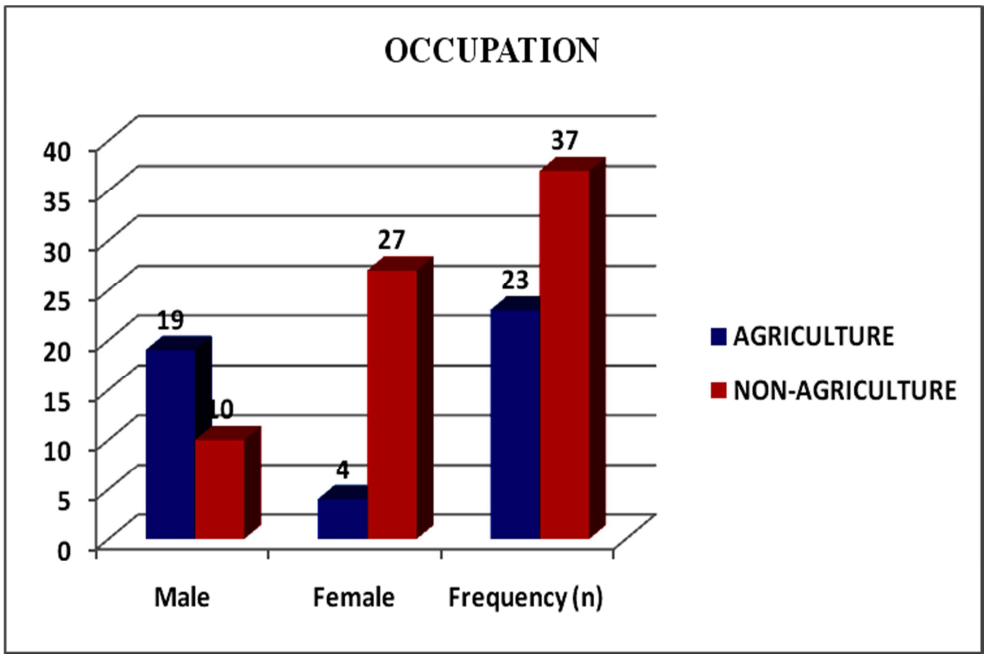


Table : 3 ROUTE OF EXPOSURE

Route	Male	Female	Frequency (n)
INHALATION	**1**	**0**	**1**
INGESTION	**28**	**31**	**59**
TOTAL	**29**	**31**	**60**

Almost all the patients are exposed to organophosphorus compounds by ingestion (n=59) except only one who has been exposed through inhalation (n=1).

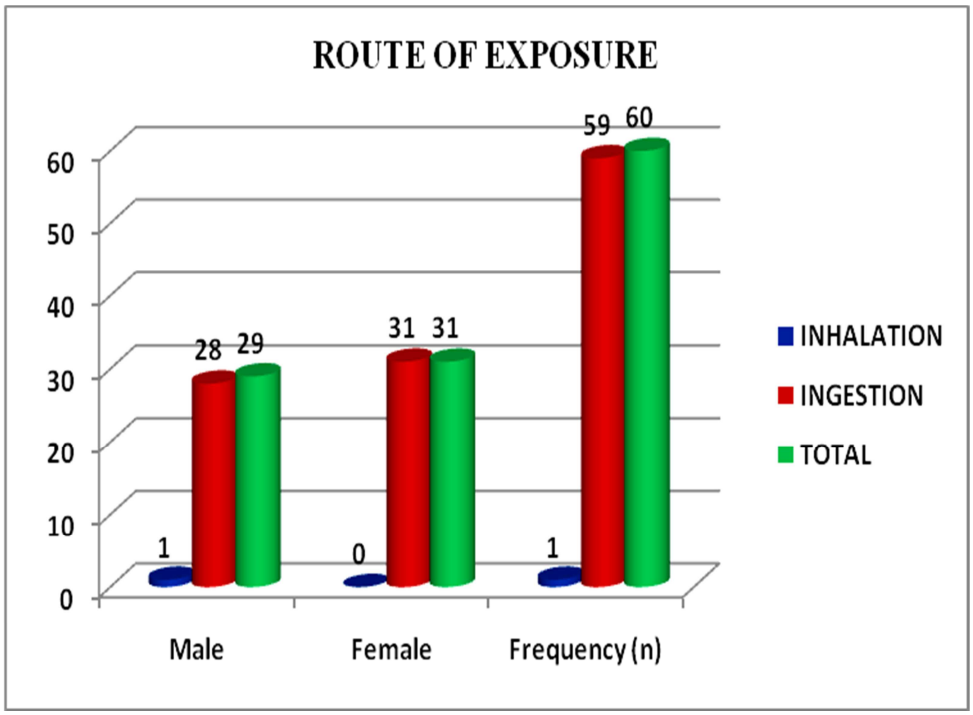


Table 4 : QUANTUM OF EXPOSURE AND OUTCOME

QUANTITY CONSUMED (ml)	OUTCOME	
	DISCHARGE	DEATH
NA	01	0
≤50 ml	29	01
51 – 100 ml	20	04
>100 ml	03	02
TOTAL	53	07

There is no clear correlation between the amount of exposure to compounds to the outcome including death (p=0.085). There are also other factors important in predicting the outcome like route of exposure, type of compounds, quantum of absorption, hydrolytic capacity, excretion, etc.,

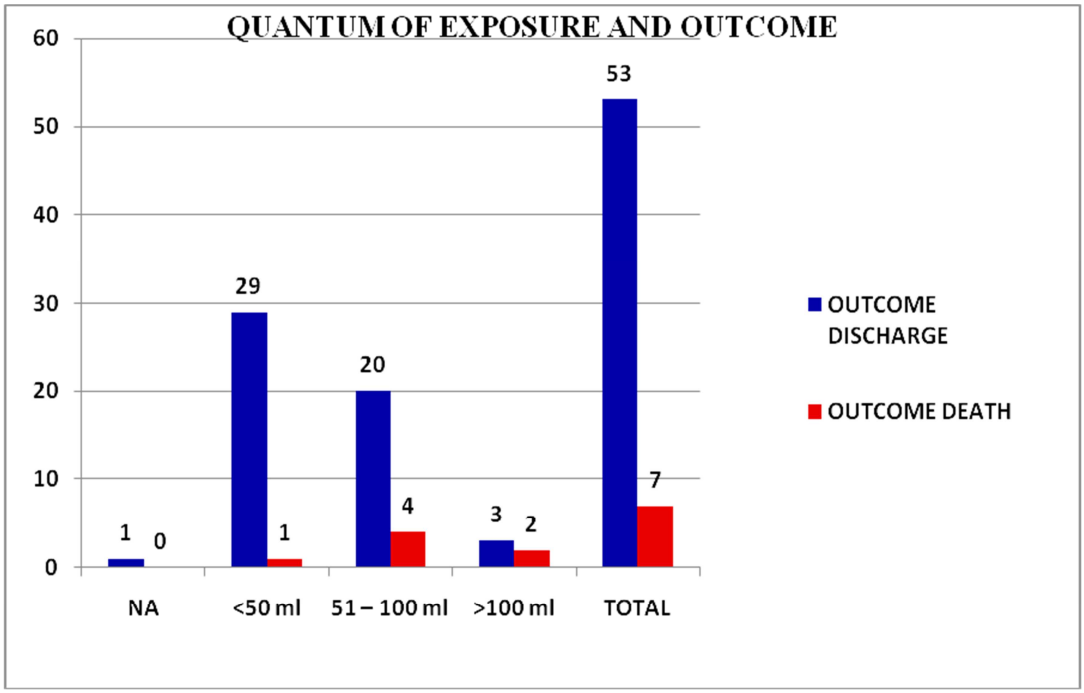


Table : 5 CLINICAL SEVERITY AND TIME OF ARRIVAL TO HOSPITAL

TIME OF ARRIVAL	CLINICAL SEVERITY			P value
	MILD	MODERATE	SEVERE	
0 – 3 Hrs	01	02	06	0.023
4 – 6 Hrs	16	13	08	
7 – 9 Hrs	05	07	0	
10 – 12 Hrs	01	01	0	
TOTAL	23	23	14	

The severity of poisoning makes the patient seeking the health care centre earlier and it seems to be significant (p = 0.023)

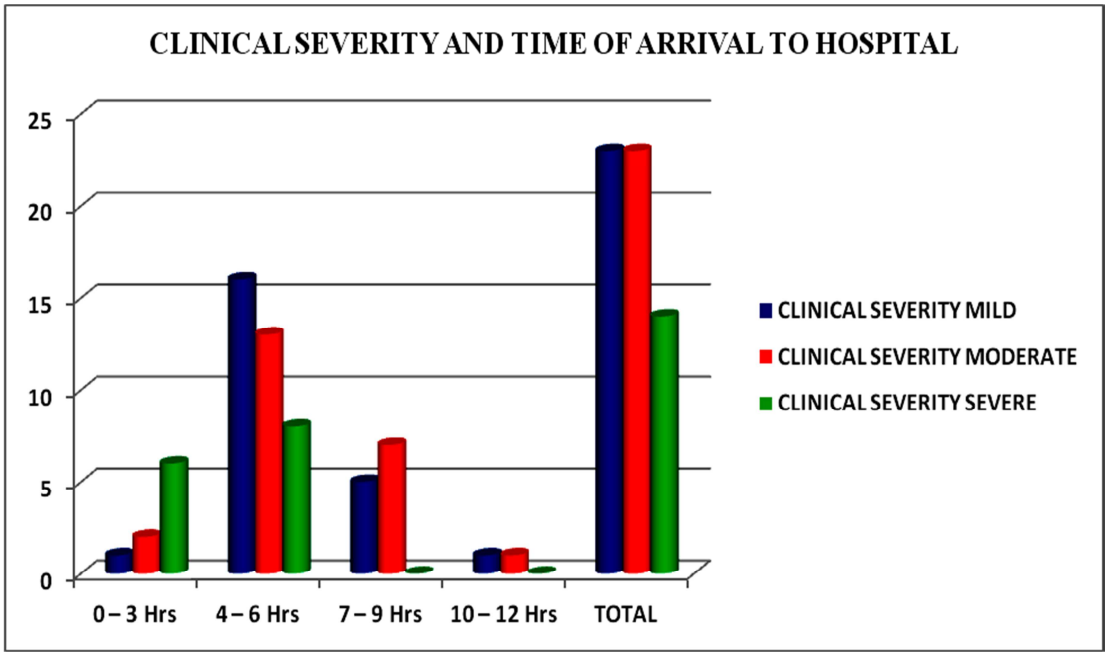


Table 6 : QUANTUM OF EXPOSURE AND CLINICAL SEVERITY BY POP SCORING

QUANTITY (ml)	CLINICAL SEVERITY			P value
	MILD	MODERATE	SEVERE	
≤50 ml	18	09	03	0.007
51 – 100 ml	04	12	08	
>100 ml	0	02	04	
TOTAL	22	23	15	

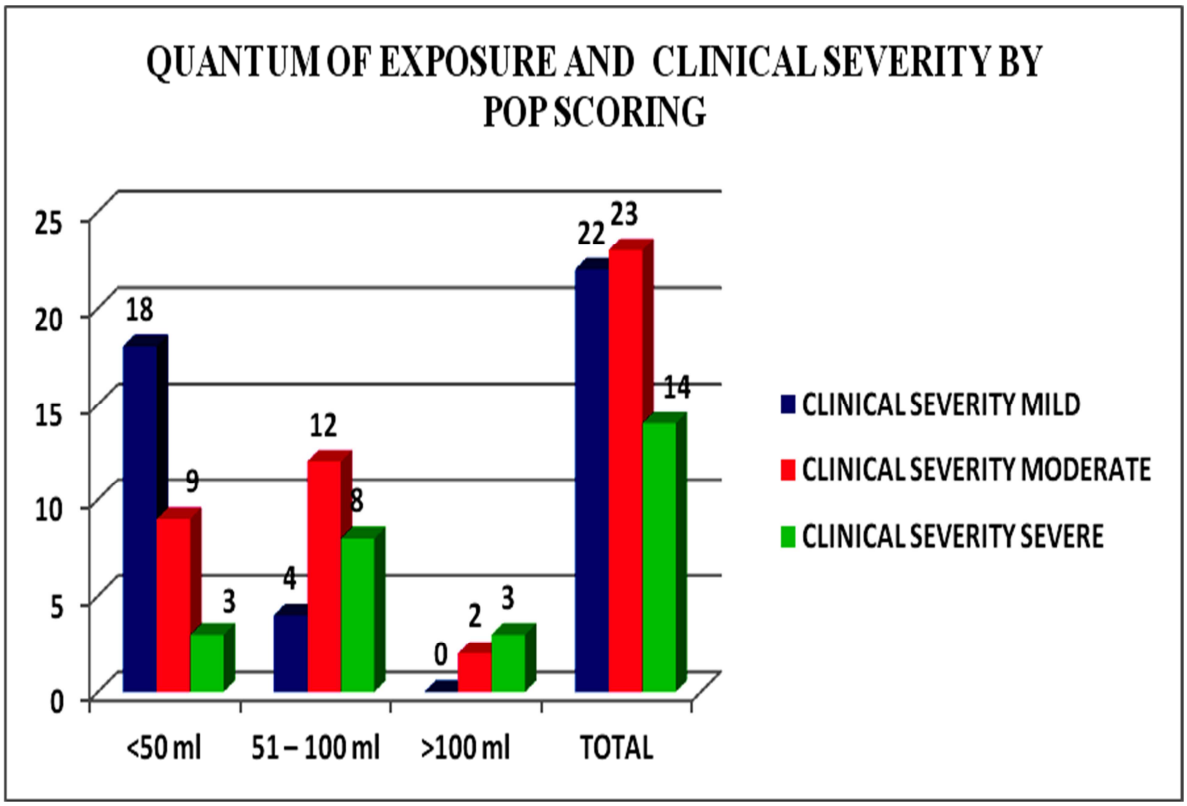


Table 7 : CLINICAL SEVERITY AND OUTCOME

CLINICAL SEVERITY	OUTCOME		P value
	DISCHARGE	DEATH	
MILD	23	0	0.085
MODERATE	20	3	
SEVERE	10	4	
TOTAL	53	7	

Most of the deaths in the study population occurred from the category of moderate and severe poisoning classified accordingly by POP score (p=0.031). Thus the assessment of clinical severity by Peradeniya Organophosphorus Poisoning scale seems reliable. Hence, it is used for the correlation of initial serum creatine kinase and magnesium levels with the complications and clinical outcome.

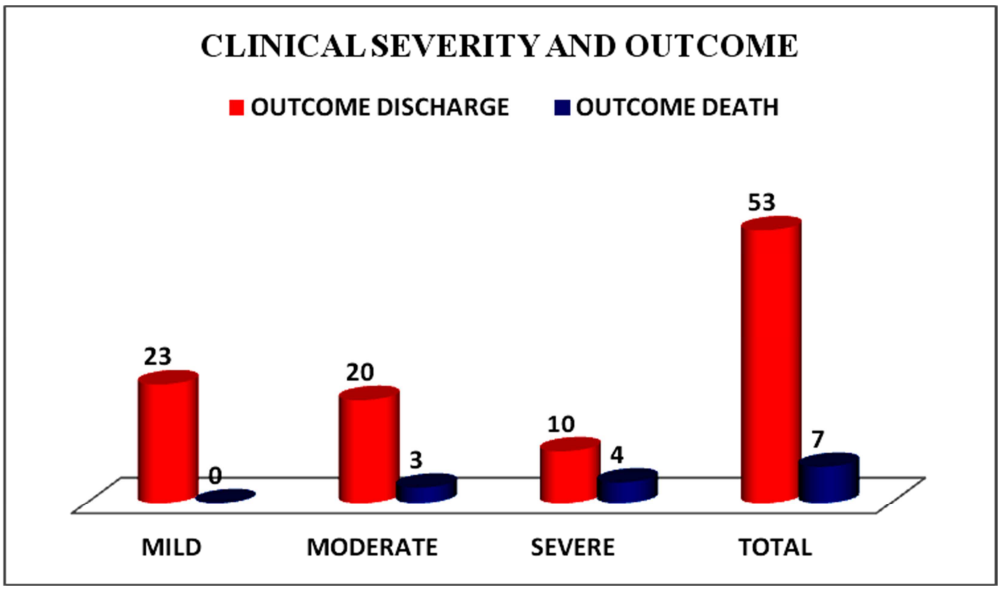


Table 8 : CLINICAL SEVERITY AND INITIAL MEAN SERUM CK VALUES

CLINICAL SEVERITY	Mean CK (IU/L)	P value
MILD	147	<0.001
MODERATE	607.2	
SEVERE	3171.2	

The clinical severity positively correlates with the initial mean serum creatine kinase levels ($p < 0.001$). Thus, the severe poisoning cases will have high serum creatine kinase levels at admission and mild poisoning have normal levels while moderate cases lie in between and is significant. This elevation of serum creatine kinase is due to the muscle fiber necrosis produced due to the high toxicity of the OPC compounds.

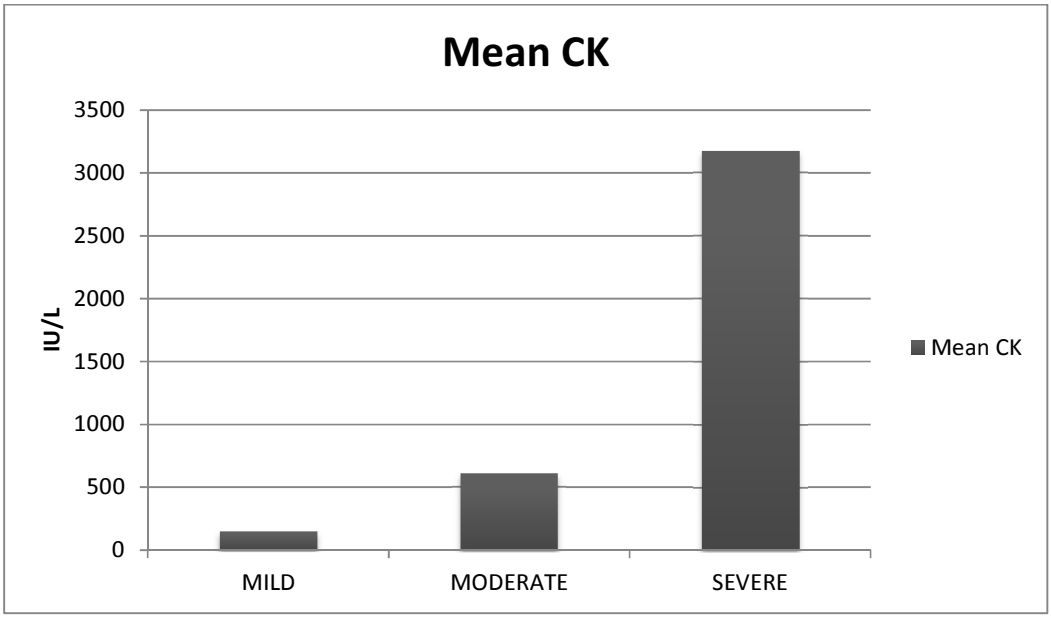


Table 9 : CLINICAL SEVERITY AND INITIAL MEAN MAGNESIUM VALUES

CLINICAL SEVERITY	Mean Magnesium (mg/dl)	P value
MILD	1.9	<0.001
MODERATE	1.64	
SEVERE	1.55	

As severity of organophosphorus poisoning is associated with the reducing levels of serum magnesium, it has negative correlation ($p < 0.001$)

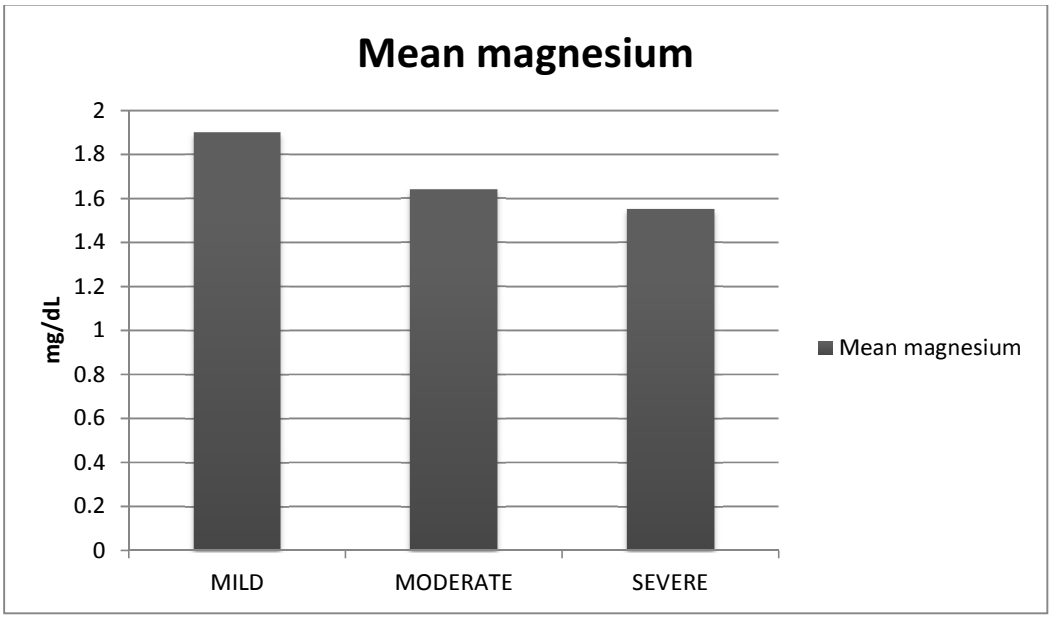


Table 10 : TIME OF ARRIVAL AND MEAN CK VALUES

TIME OF ARRIVAL (hrs)	Mean CK values(IU/L)	P value
0 – 3	3010.6	0.002
4 – 6	748.3	
7 – 9	550.9	
10 – 12	175	

The patients seeking hospital earlier i.e. within 3 hours of exposure had elevated serum Creatine kinase levels and it makes significant correlation ($p = 0.002$).

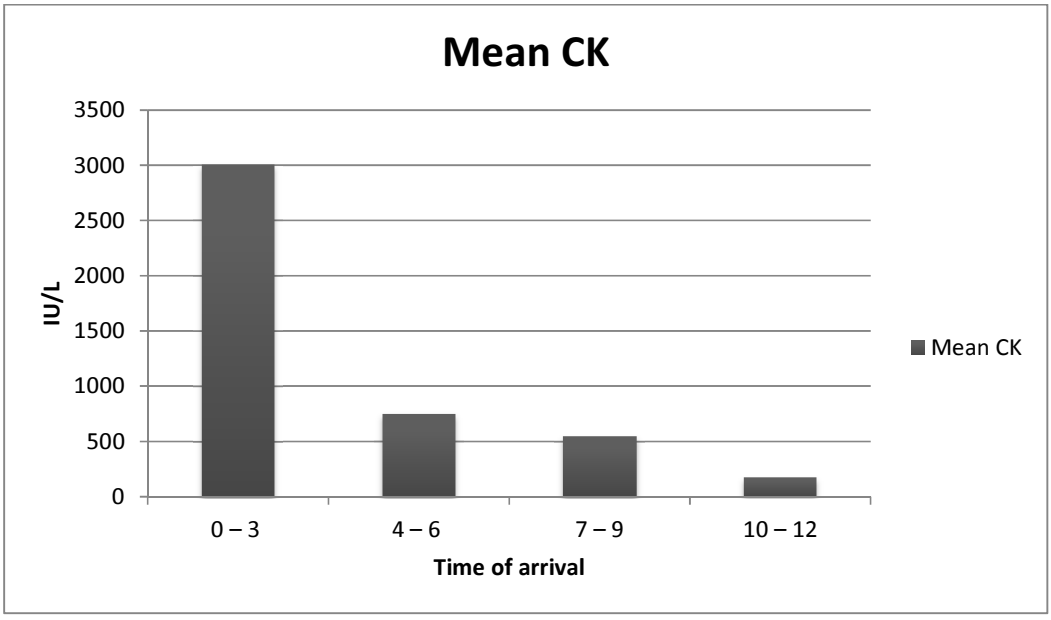


Table 11 : TIME OF ARRIVAL AND MEAN MAGNESIUM VALUES

TIME OF ARRIVAL (hrs)	Mean Mg values(mg/dl)	P value
0 – 3	1.58	0.108
4 – 6	1.74	
7 – 9	1.78	
10 – 12	1.80	

Initial serum magnesium levels at admission has no correlation with time of arrival to the hospital (p = 0.108)

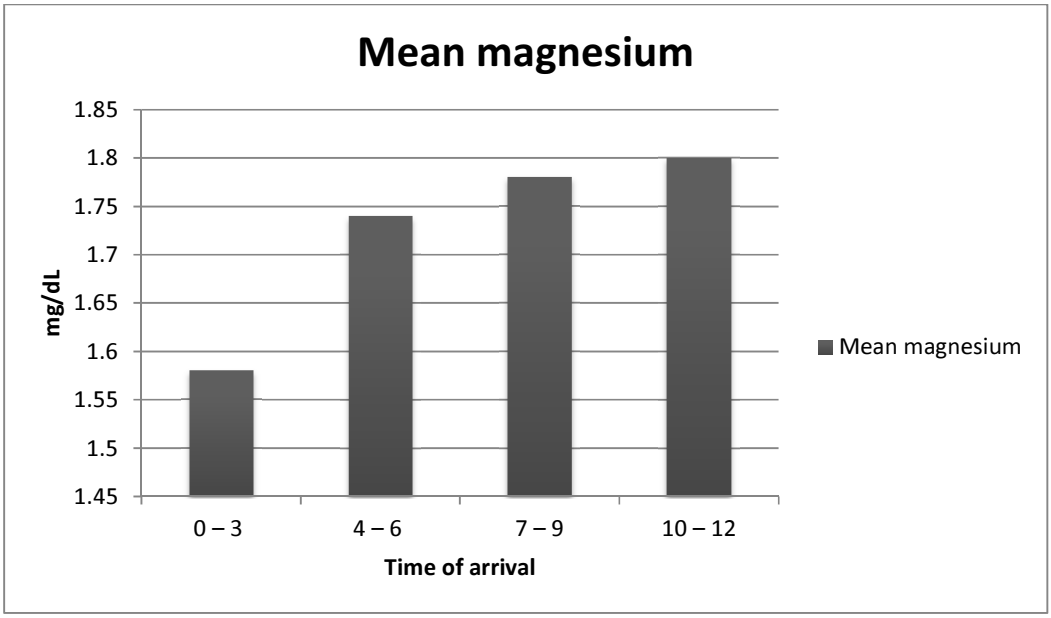


Table 12 : QUANTUM OF EXPOSURE AND INITIAL MEAN CK VALUES

AMOUNT OF POISON (ml)	INITIAL MEAN CK LEVELS(IU/L)	P value
≤50 ml	489.4	0.049
51 – 100 ml	1591.8	
> 100 ml	920.4	

The quantum of exposure is directly proportional to the increased serum creatine kinase levels (p = 0.049)

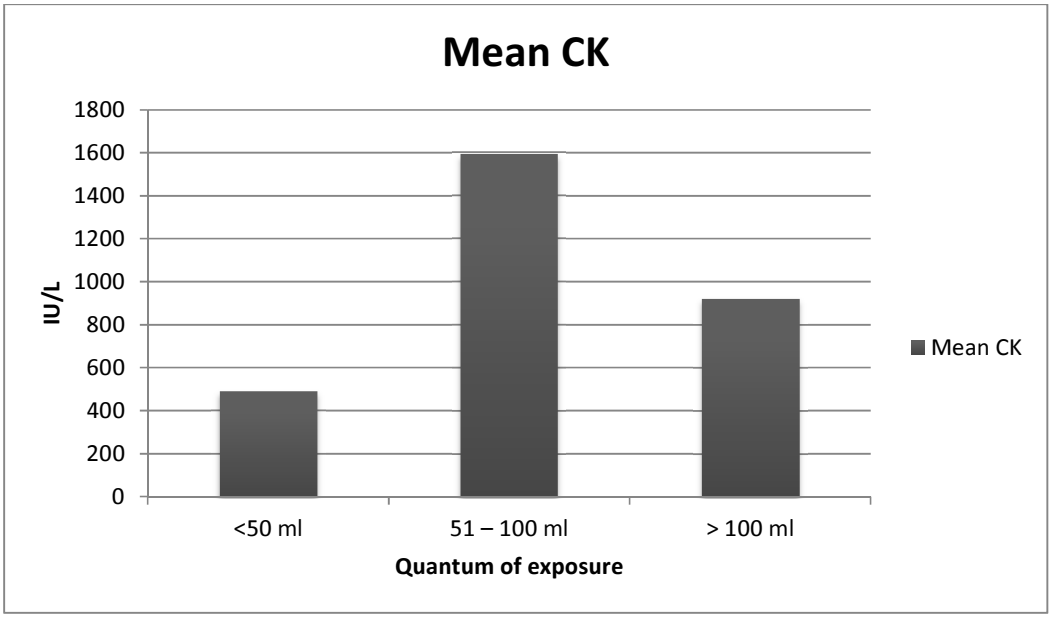


Table 13 : QUANTUM OF EXPOSURE AND INITIAL MEAN MAGNESIUM VALUES

AMOUNT OF POISON (ml)	INITIAL MEAN MAGNESIUM LEVELS(mg/dl)	P value
≤50 ml	1.83	<0.001
51 – 100 ml	1.62	
> 100 ml	1.66	

The quantity of compounds exposed negatively correlate with the serum magnesium levels. ($p < 0.001$)

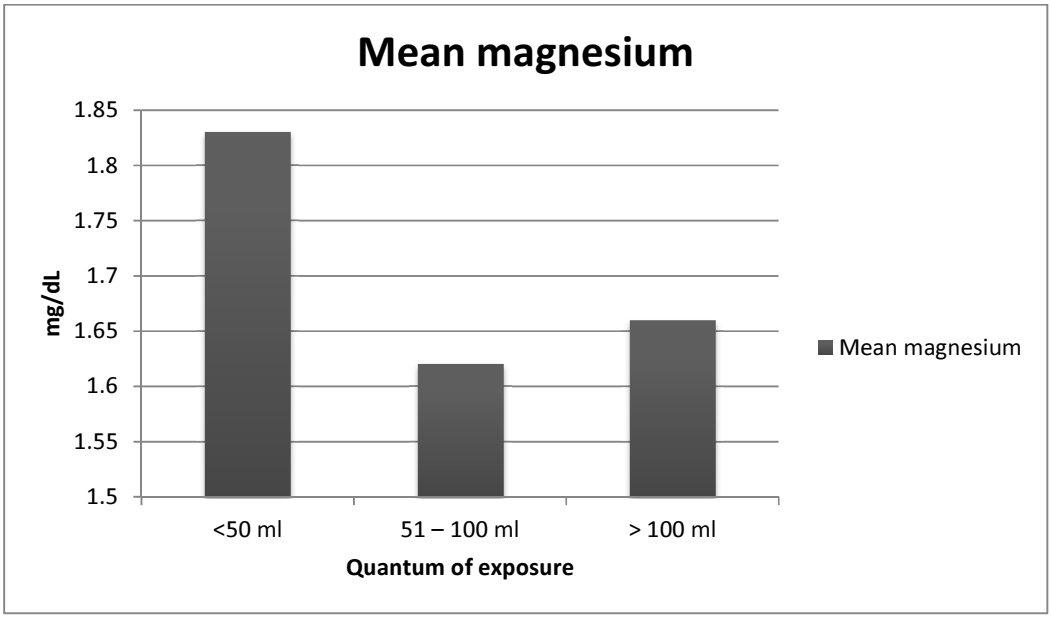


Table 14 : CLINICAL SEVERITY AND DURATION OF HOSPITAL STAY

CLINICAL SEVERITY	DURATION OF HOSPITAL STAY (DAYS)				P value
	<7	8 - 14	15 – 21	>21	
MILD	22	01	01	0	<0.001
MODERATE	05	11	05	2	
SEVERE	0	02	05	7	

The duration of hospital stay positively correlates with the clinical severity at admission (p <0.001). Hence, the patients admitted as severe poisoning clinically, will have prolonged hospital stay due to the development of complications like ventilator requirement, dialysis for renal failure, etc.,

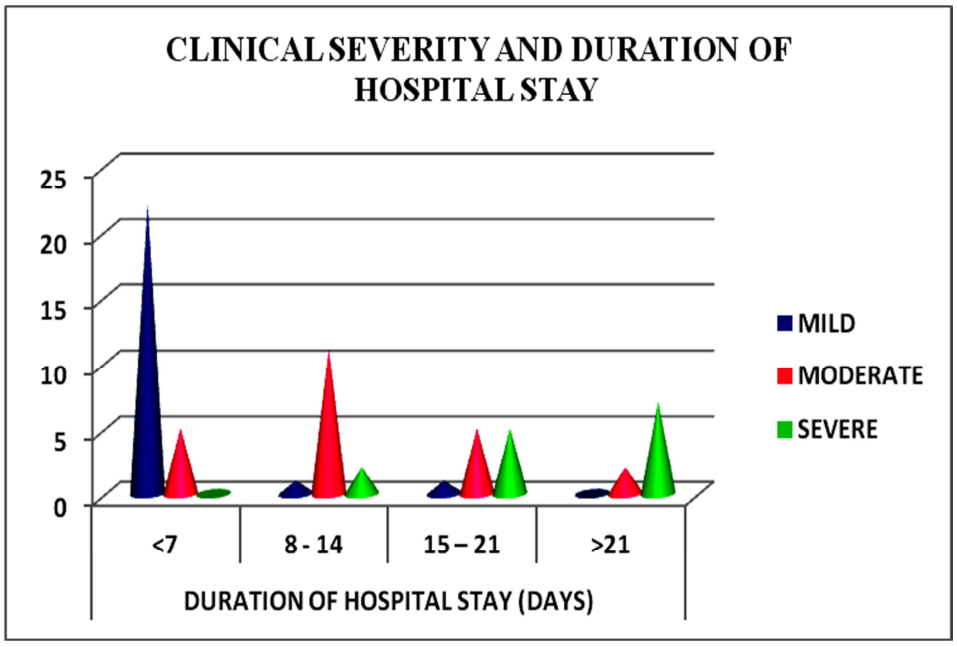


Table 15 : DURATION OF HOSPITAL STAY AND INITIAL MEAN

CK VALUES

DURATION OF STAY (DAYS)	INITIAL MEAN CK LEVELS(IU/L)	P value
<7	**188.4**	**<0.001**
8 – 14	**774.2**	
15 – 21	**890.4**	
>21	**4088.6**	

In patients with raised serum creatine kinase levels, at admission, prolonged hospital stay can be expected due to development of various complications, as it has positive correlation (p <0.001)

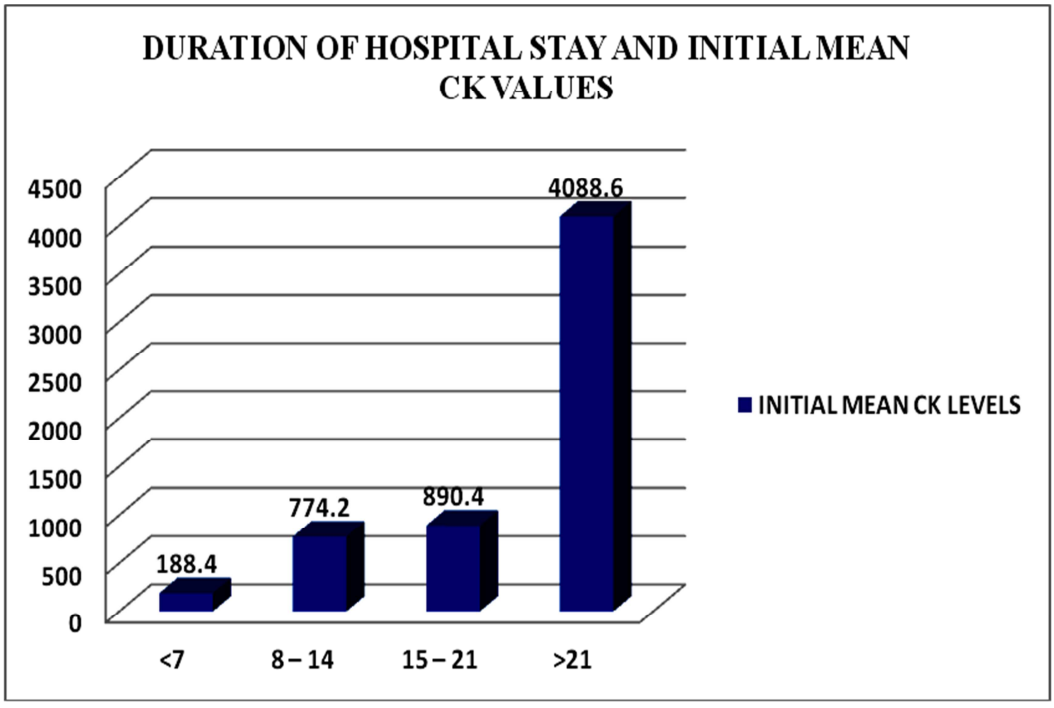


Table 16 : DURATION OF HOSPITAL STAY AND INITIAL MEAN

MAGNESIUM VALUES

DURATION OF STAY (DAYS)	INITIAL MEAN MAGNESIUM LEVELS(mg/dl)	P value
<7	1.85	<0.001
8 – 14	1.68	
15 – 21	1.63	
>21	1.52	

Reduced serum magnesium levels at the time of admission leads to prolonged hospital stay as it has negative correlation (p <0.001)

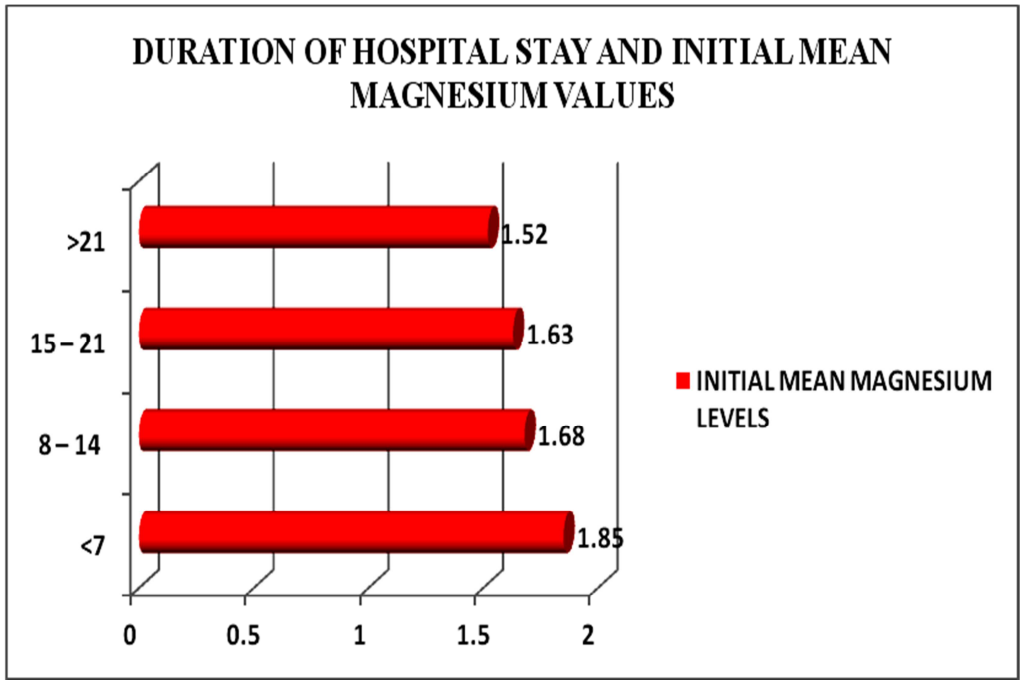


Table 17 : FREQUENCY OF SUBSTANCE EXPOSED

Sl.No.	COMPOUNDS	FREQUENCY
1.	DIAZINON	01
2.	QUINALPHOS	01
3.	CHLORPYRIFOS	16
4.	DICHLOROVAS	01
5.	DIMETHOATE	10
6.	MONOCHROTOPHOS	9
7.	PROPENOPHOS	08
8.	TEMIPHOS	06
9.	TRIAZOPHOS	08

Most of the patients in this series consumed Chlorpyrifos (n=16) and Dimethoate (n=10). But, the type of poison does not contribute to severity or mortality.

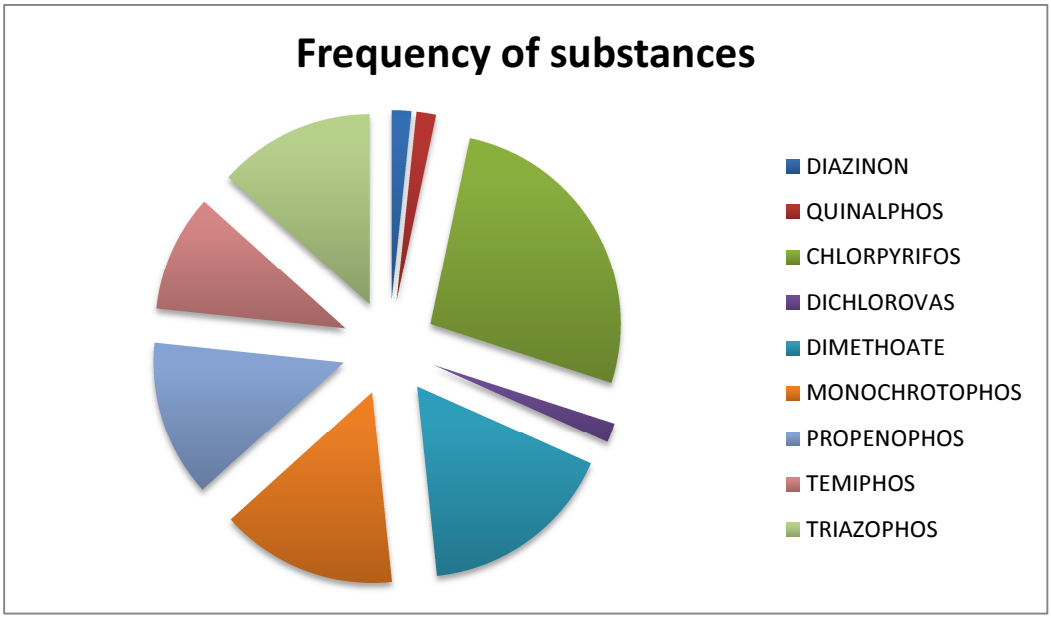


Table 18 : FREQUENCY OF RENAL FAILURE WITH INITIAL SERUM CK VALUES COMPARED TO CLINICAL SEVERITY

CLINICAL SEVERITY	RENAL FAILURE(n)	MEAN INITIAL CK VALUES(IU/L)	P value
MILD (n = 23)	0	0	0.002
MODERATE (n = 23)	9	526.3	
SEVERE (n = 14)	5	4249	

The incidence of renal failure positively correlates with the raised values of serum creatine kinase at admission (p = 0.002)

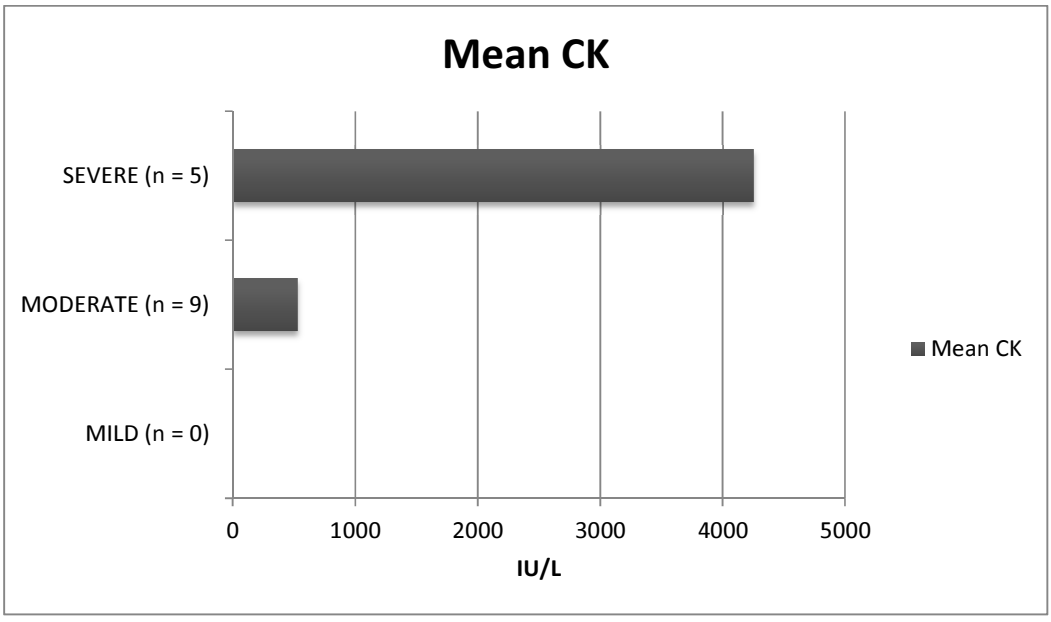


Table 19 : FREQUENCY OF RENAL FAILURE WITH INITIAL SERUM Mg VALUES COMPARED TO CLINICAL SEVERITY

CLINICAL SEVERITY	RENAL FAILURE(n)	MEAN INITIAL MgVALUES(mg/dl)	P value
MILD (n = 23)	0	0	0.153
MODERATE (n = 23)	9	1.67	
SEVERE (n = 14)	5	1.56	

Though the incidence of renal failure is common in patients with initial reduced serum magnesium levels, it does not have significance (p = 0.153).

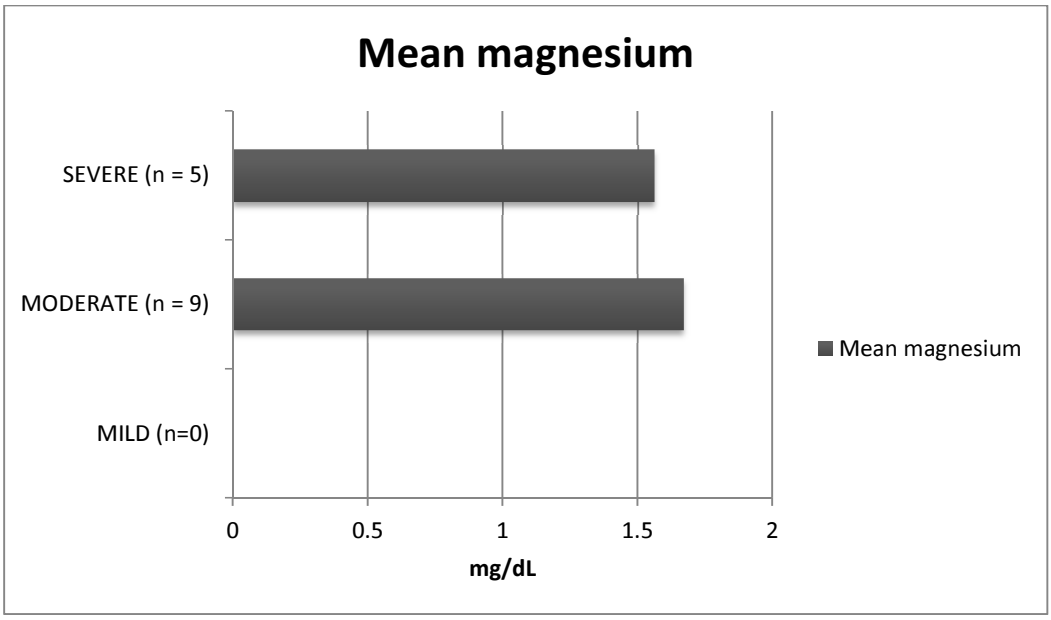


Table 20 : CLINICAL SEVERITY AND MEAN pH VALUES

CLINICAL SEVERITY	MEAN pH	P value
MILD	7.36	0.028
MODERATE	7.35	
SEVERE	7.35	

Increasing severity of organophosphorus poisoning at admission negatively correlates with arterial pH values and its complications (p = 0.028)

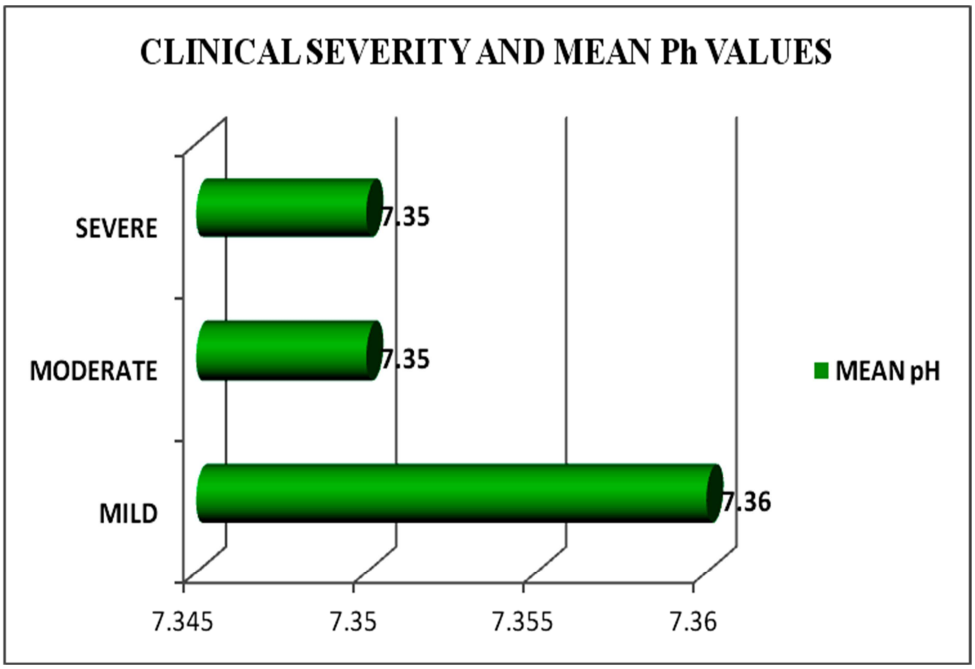


Table 21 : ARRYTHMIAS AND INITIAL MEAN CK LEVELS COMPARED TO CLINICAL SEVERITY

CLINICAL SEVERITY	ARRYTHMIAS (n)	INITIAL SERUM MEAN CK LEVELS (IU/L)	P value
MILD (n = 23)	0	0	0.624
MODERATE (n = 23)	1	1320.0	
SEVERE (n = 14)	2	2472.5	

Though the patients who developed arrhythmias had come under moderate and severe poisoning category, it carries no significant correlation. Also, the incidence of arrhythmias does not correlate with the initial serum creatine kinase levels (p = 0.624).

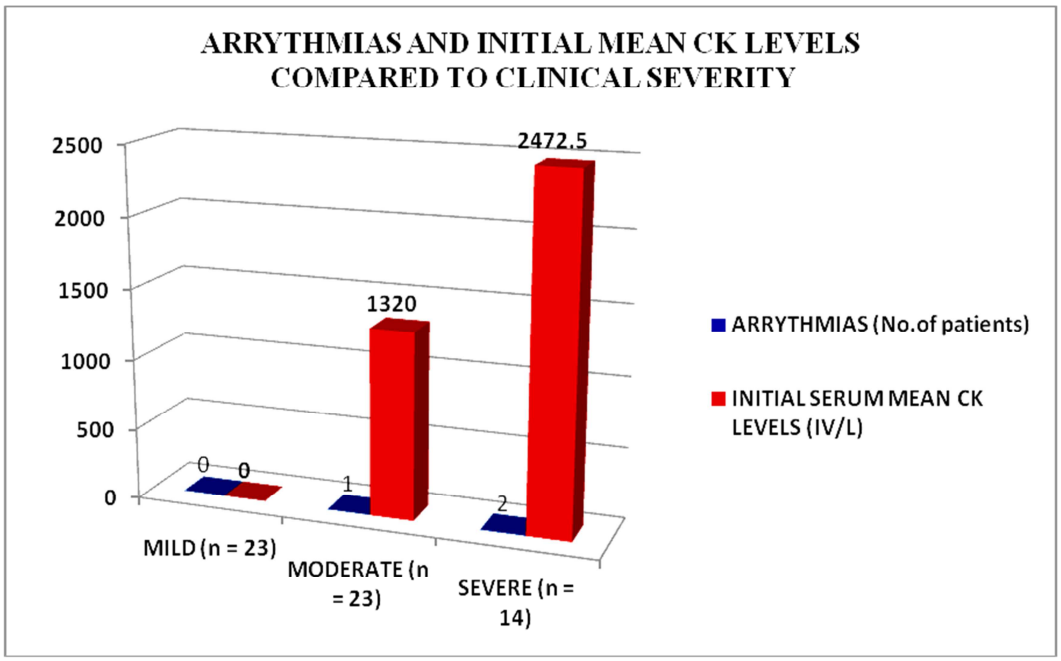


Table 22 : ARRYTHMIAS AND INITIAL MAGNESIUM LEVELS COMPARED TO CLINICAL SEVERITY

CLINICAL SEVERITY	ARRYTHMIAS (n)	INITIAL MEAN SERUM MAGNESIUM LEVELS (mg/dl)	P value
MILD (n = 23)	0	0	0.333
MODERATE (n = 23)	01	1.5	
SEVERE (n = 14)	02	1.6	

The incidence of arrhythmias does not correlate with the initial serum magnesium levels (p = 0.333)

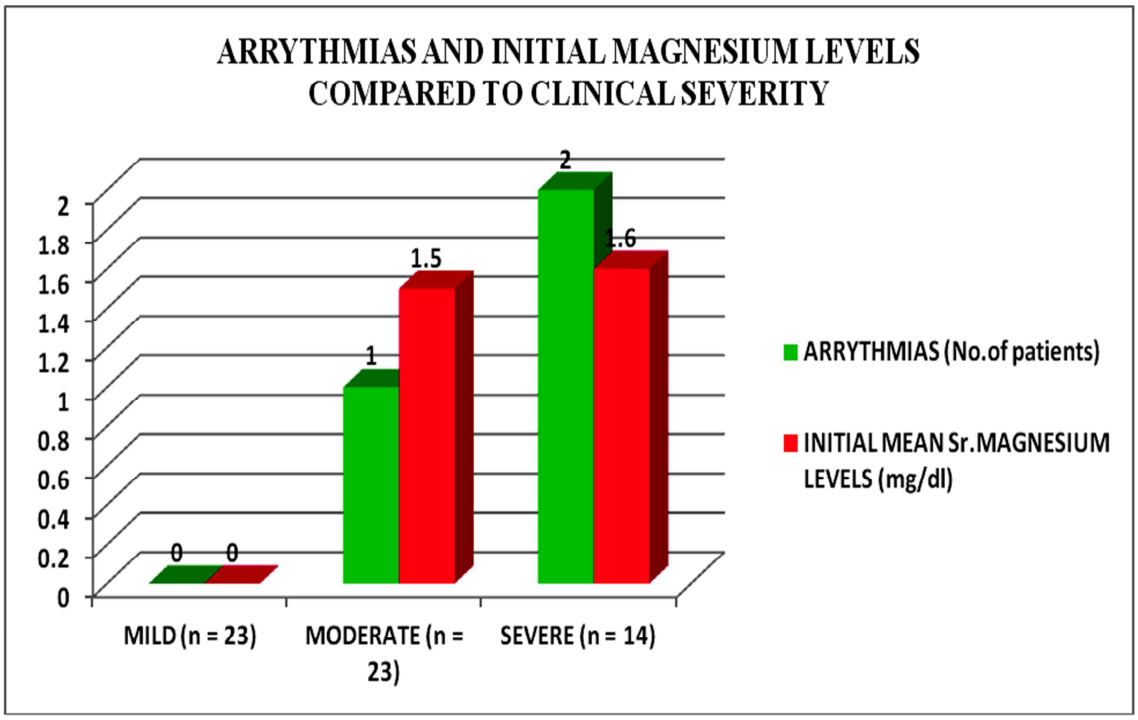


Table 23 : ATROPINE DOSE REQUIREMENT AND CLINICAL SEVERITY

ATROPINE DOSE REQUIREMENT (No. of vials)	CLINICAL SEVERITY		
	MILD	MODERATE	SEVERE
<10	14	01	0
11 – 20	08	05	01
21 – 30	01	12	04
31 – 40	0	05	05
41 – 50	0	0	03
>50	0	0	01

Patients admitted as severe poisoning category will require large doses of atropine as revealed from the table above. Hence, we conclude that the clinical severity as estimated from POP score is worth taking to correlate with the laboratory parameters and outcome in acute organophosphorus poisoning.

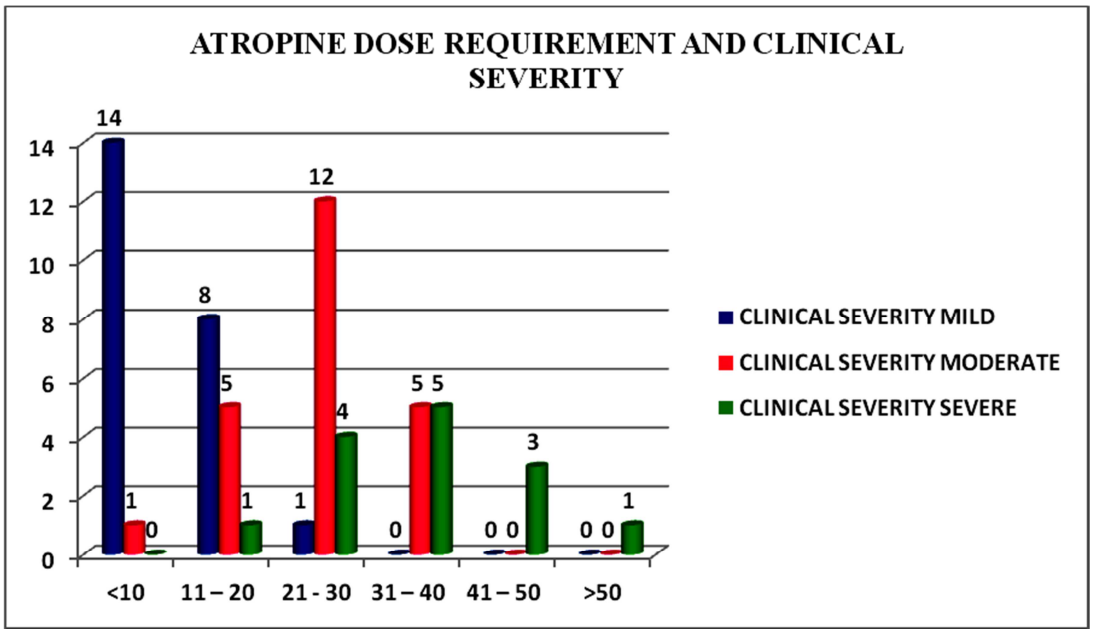


Table 24 : ATROPINE DOSE REQUIREMENT AND INITIAL MEAN CK LEVELS

ATROPINE DOSE REQUIREMENT (No. of vials)	INITIAL MEAN CK (IU/L)	P value
<10	142.8	<0.001
11 – 20	338.3	
21 – 30	881.1	
31 – 40	1727.5	
41 – 50	4804.0	
>50	8200.0	

The comparison of atropine dose requirement and initial mean serum creatine kinase is significant with the positive correlation (p <0.001)

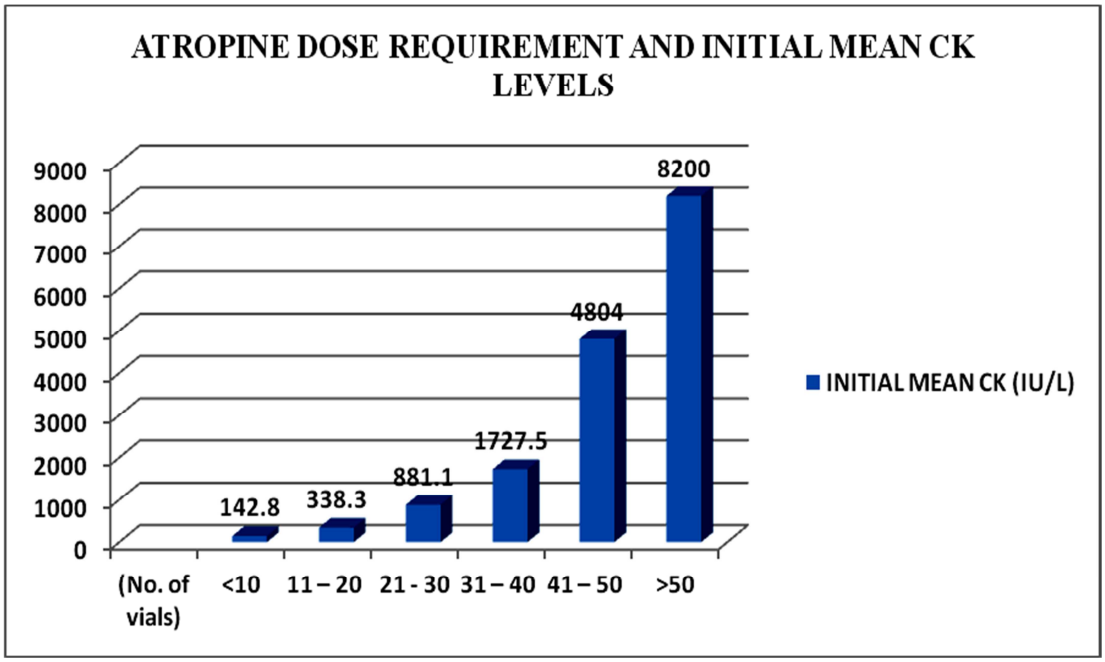


Table 25 : ATROPINE DOSE REQUIREMENT AND INITIAL MEAN MAGNESIUM LEVELS

ATROPINE DOSE REQUIREMENT (No. of vials)	INITIAL MEAN Mg (mg/dl)	P value
<10	1.90	<0.001
11 – 20	1.76	
21 – 30	1.66	
31 – 40	1.64	
41 – 50	1.43	
>50	1.33	

The comparison of atropine dose requirement and initial mean serum magnesium level is significant with the negative correlation ($p < 0.001$) i.e. patients with low serum magnesium level at admission will require large doses of atropine.

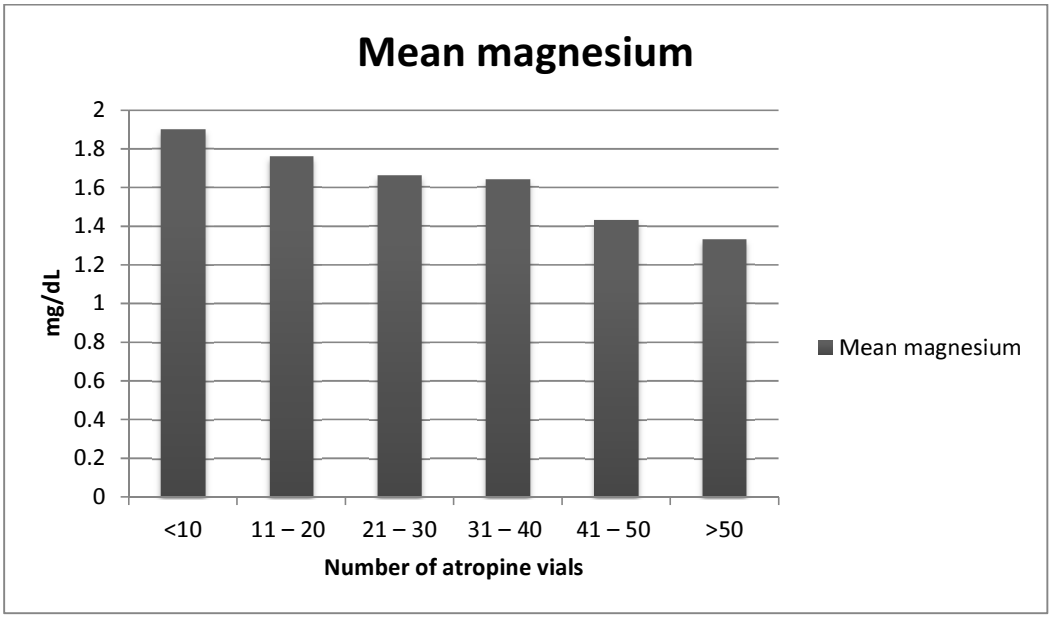


Table 26 : SEIZURES AND INITIAL SERUM CK LEVELS COMPARED TO CLINICAL SEVERITY

CLINICAL SEVERITY	SEIZURE(n)	INITIAL MEAN CK VALUE (IU/L)
MILD (n = 23)	0	0
MODERATE (n = 23)	1	810
SEVERE (n = 14)	0	0

Only one patient from moderate poisoning category developed seizures with mildly elevated serum creatine kinase level at admission and it cannot be considered as significant.

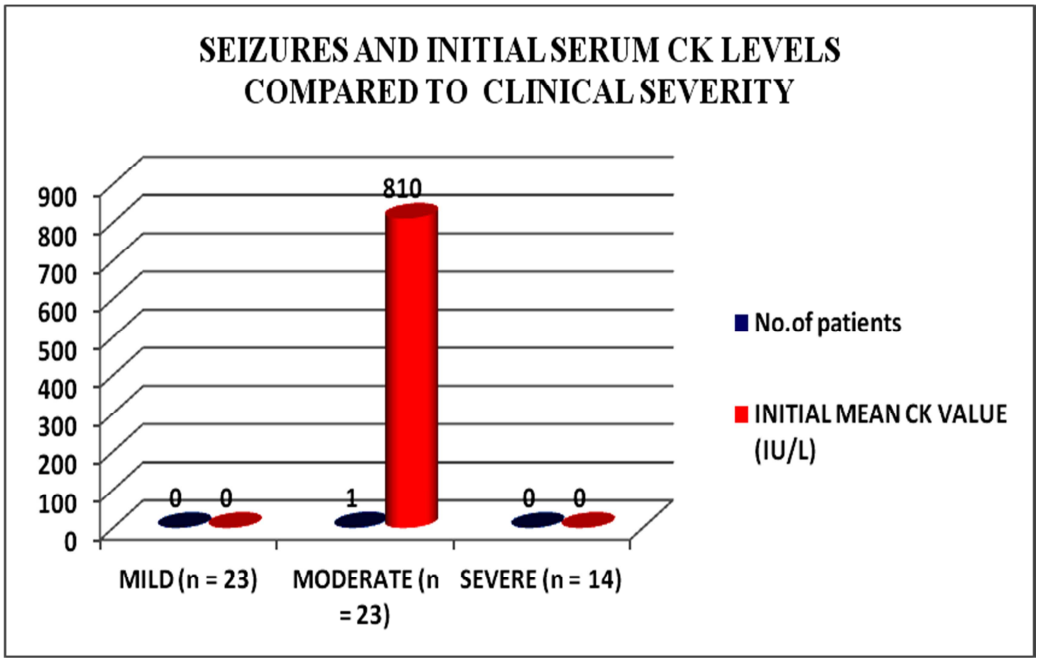


Table 27 : SEIZURES AND INITIAL SERUM MAGNESIUM LEVELS COMPARED TO CLINICAL SEVERITY

CLINICAL SEVERITY	SEIZURE(n)	INITIAL MEAN SERUM MAGNESIUM VALUE (mg/dl)
MILD (n = 23)	0	0
MODERATE (n = 23)	1	1.5
SEVERE (n = 14)	0	0

Patient who developed seizures, belonging to moderate poisoning category, had the initial serum magnesium value of 1.5 mg/dl and it cannot be considered for correlation.

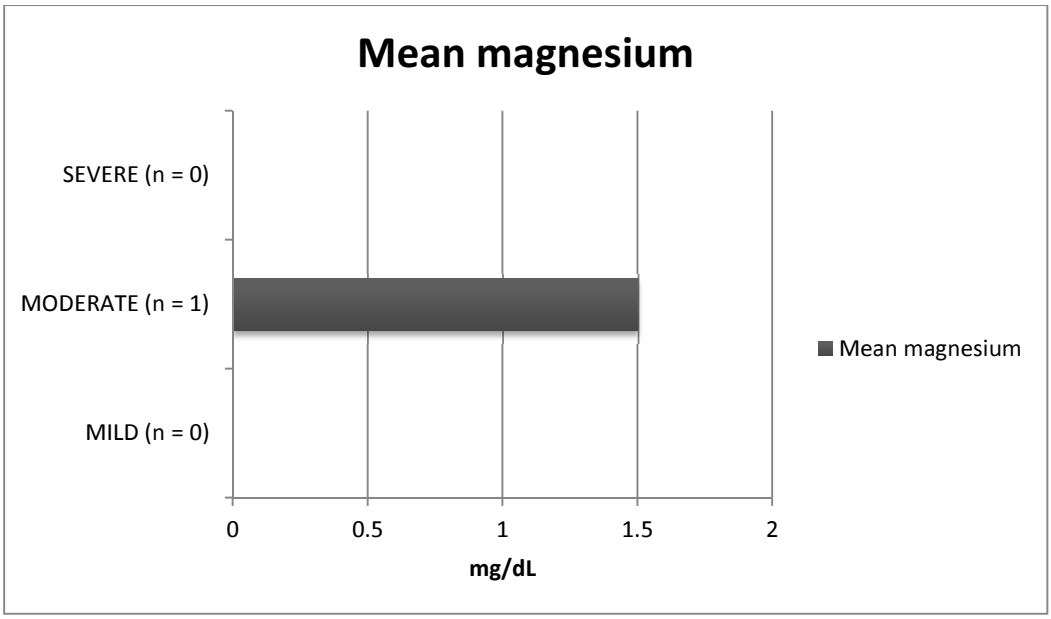


Table 28 : COINCIDENCE OF COMA AND INITIAL SERUM CK LEVELS TO CLINICAL SEVERITY

CLINICAL SEVERITY	COMA (n)	INITIAL MEAN SERUM CK VALUES (IU/L)
MILD (n = 23)	0	0
MODERATE (n = 23)	0	0
SEVERE (n = 14)	3	4790

From the table, we conclude that three patients from severe poisoning category went into comatose state, with the elevated mean serum creatine kinase levels, but it could not be correlated.

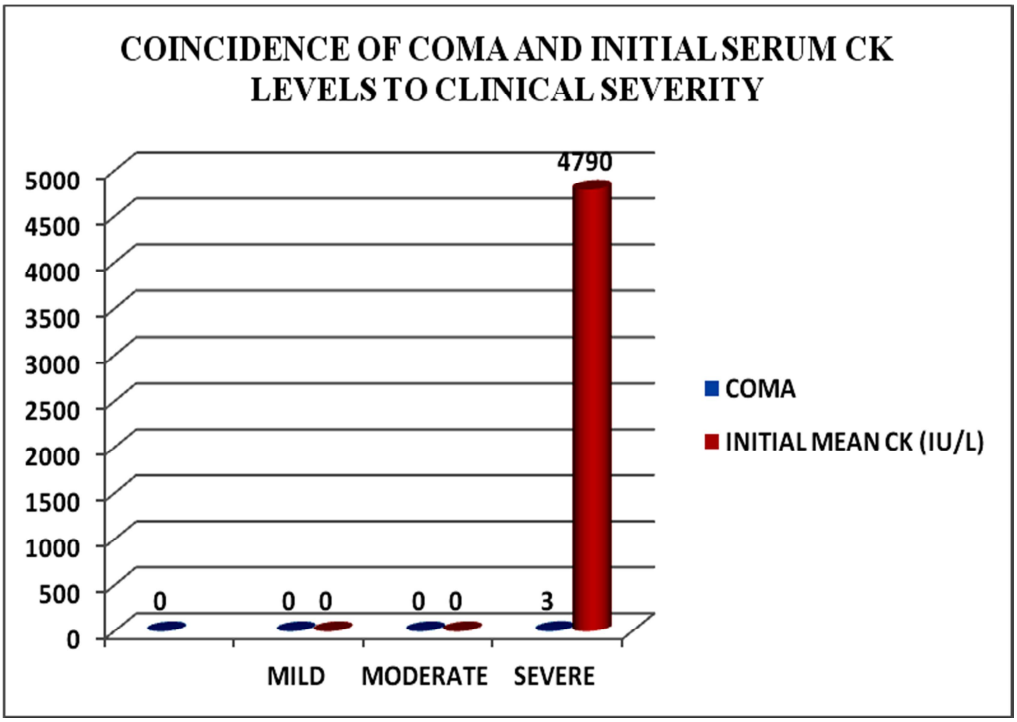


Table 29 : COINCIDENCE OF COMA AND INITIAL MEAN MAGNESIUM LEVELS COMPARED TO CLINICAL SEVERITY

CLINICAL SEVERITY	COMA (n)	INITIAL MEAN SERUM MAGNESIUM VALUE (mg/dl)
MILD (n = 23)	0	0
MODERATE (n = 23)	0	0
SEVERE (n = 14)	3	1.48

Among the severe poisoning category, three patients went into comatose state with low mean serum magnesium levels.

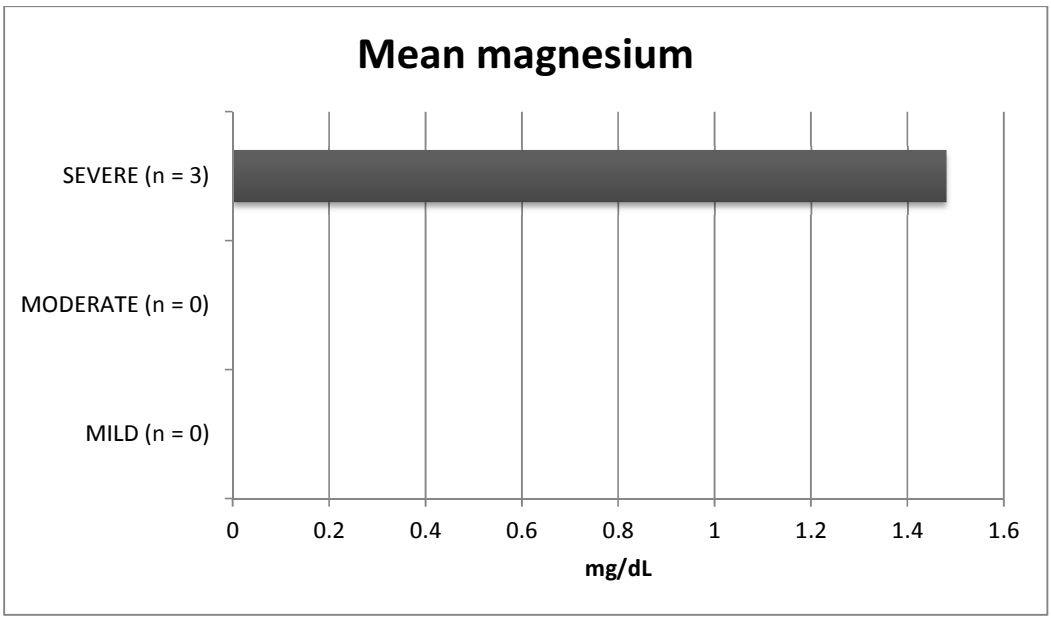


Table 30 : MECHANICAL VENTILATION REQUIREMENT AND INITIAL MEAN SERUM CK VALUES COMPARED TO CLINICAL SEVERITY

CLINICAL SEVERITY	MECHANICAL VENTILATION (n)	INITIAL MEAN CK LEVELS (IU/L)	P value
MILD (n = 23)	01	162	0.005
MODERATE (n = 23)	14	716.9	
SEVERE (n = 14)	13	3238.2	

The initial serum creatine kinase levels positively correlates with the requirement of mechanical ventilation in due course. (p = 0.005).

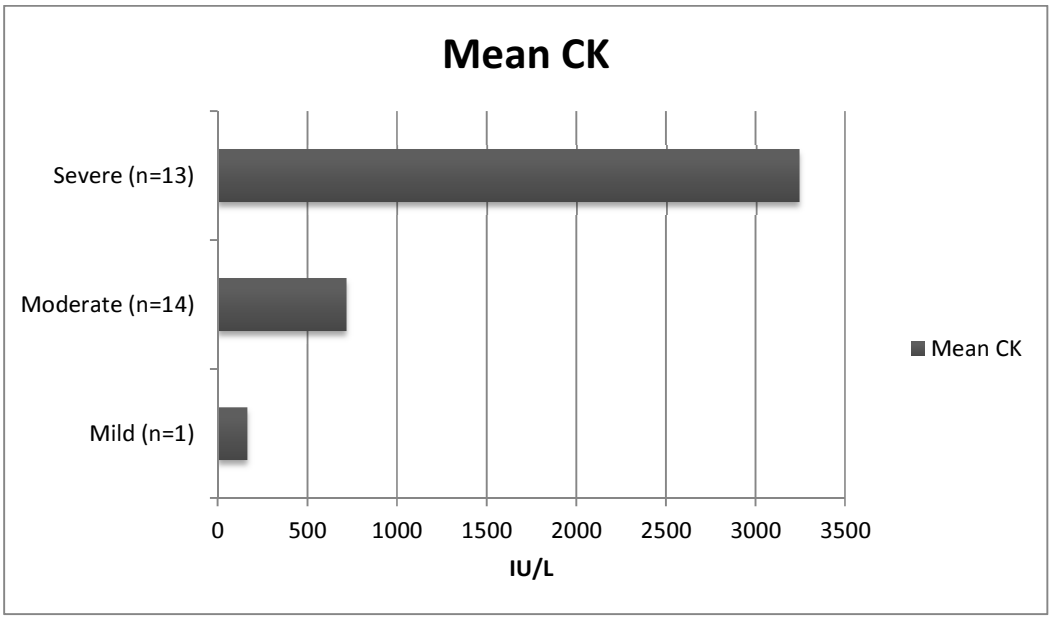


Table 31 : MECHANICAL VENTILATION REQUIREMENT AND

INITIAL MEAN MAGNESIUM VALUES COMPARED

TO CLINICAL SEVERITY

CLINICAL SEVERITY	MECHANICAL VENTILATION (n)	INITIAL MEAN MAGNESIUM LEVELS (mg/dl)	P value
MILD (n = 23)	01	1.9	0.008
MODERATE (n = 23)	14	1.66	
SEVERE (n = 14)	13	1.59	

Those with the low initial serum magnesium levels will have more requirements of mechanical ventilation and its correlation is significant. (p = 0.008).

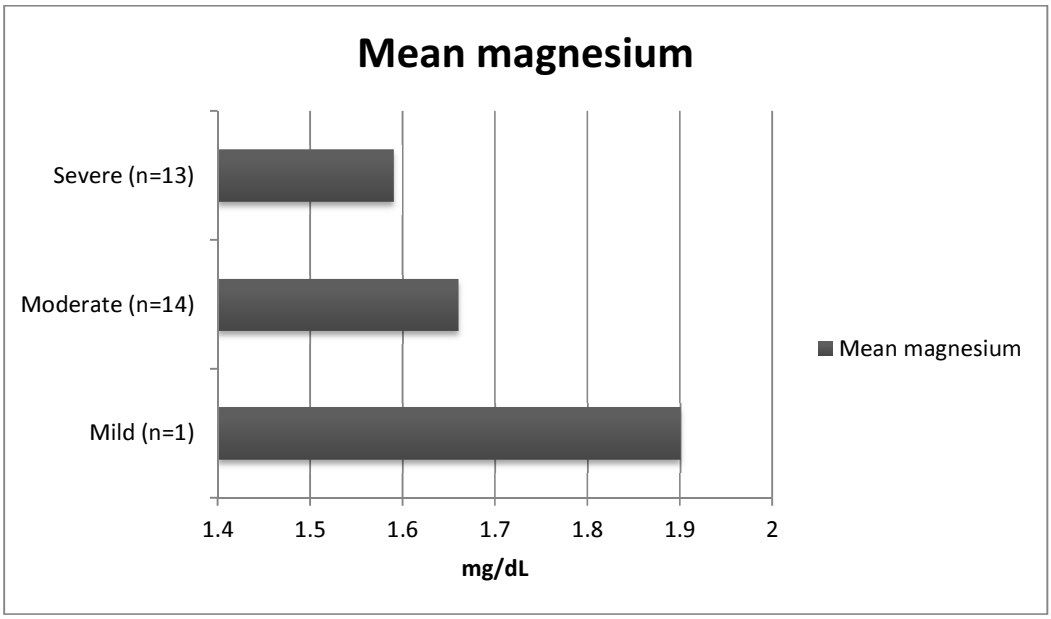


Table 32 : INTERMEDIATE SYNDROME AND INITIAL MEAN SERUM CK VALUES COMPARED TO CLINICAL SEVERITY

CLINICAL SEVERITY	INTERMEDIATE SYNDROME (n)	INITIAL MEAN CK LEVELS (IU/L)	P value
MILD (n = 23)	01	135	0.005
MODERATE (n = 23)	05	704	
SEVERE (n = 14)	04	2173	

The incidence of intermediate syndrome correlates with the categorization of clinical severity . It also has meaningful significance comparing to the initial serum creatine kinase levels (p = 0.005).

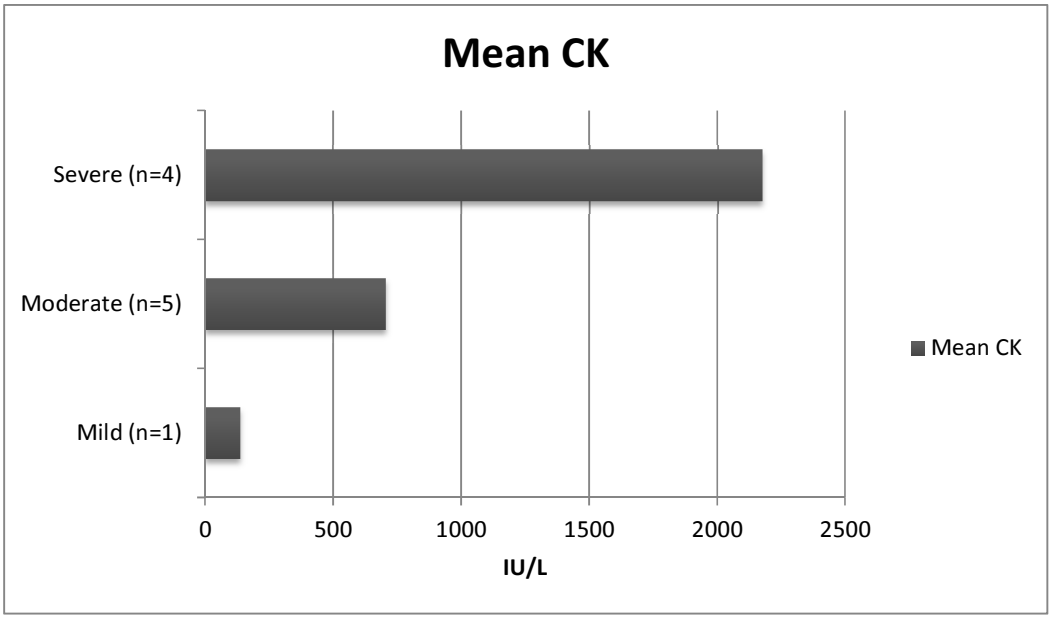


Table 33 : INTERMEDIATE SYNDROME AND INITIAL MEAN MAGNESIUM VALUES COMPARED TO CLINICAL SEVERITY

CLINICAL SEVERITY	INTERMEDIATE SYNDROME (n)	INITIAL MEAN MAGNESIUM LEVELS (mg/dl)	P value
MILD (n = 23)	01	1.6	0.141
MODERATE (n = 23)	05	1.67	
SEVERE (n = 14)	04	1.50	

The incidence of intermediate syndrome among the study population does not correlate with the initial serum magnesium levels (p = 0.141).

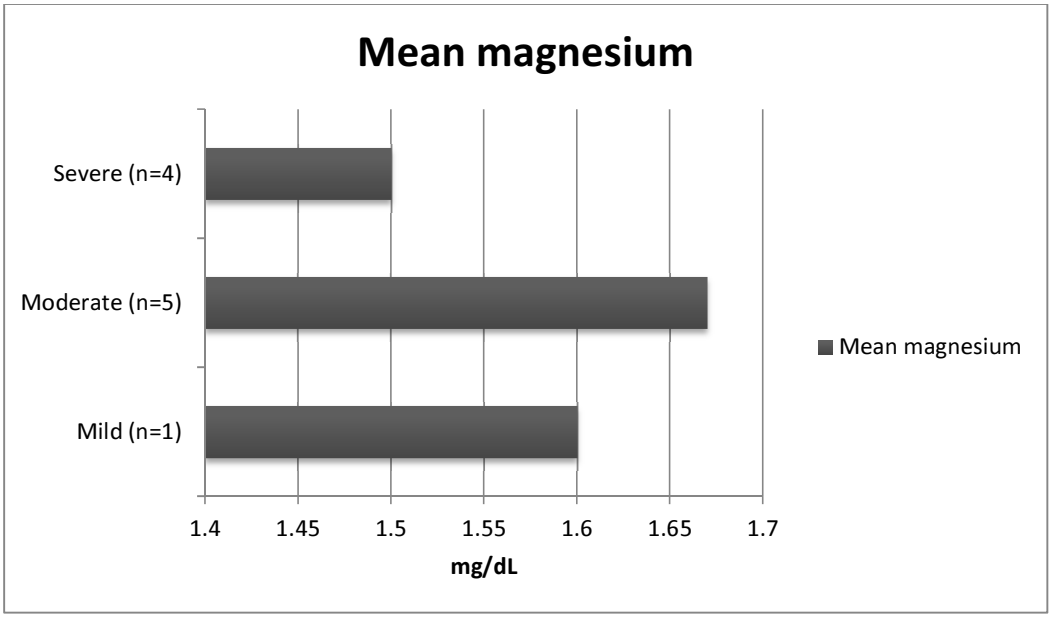


Table 34 : INCIDENCE OF DEATH AND INITIAL MEAN SERUM CK VALUES COMPARED TO CLINICAL SEVERITY

CLINICAL SEVERITY	DEATH (n)	INITIAL MEAN CK LEVELS (IU/L)	P value
MILD (n = 23)	0	0	0.005
MODERATE (n = 23)	03	1200.66	
SEVERE (n = 14)	04	3503.75	

Death rate increases in both moderate and severe poisoning and it also positively correlates with initial mean serum creatine kinase levels. (p = 0.005).

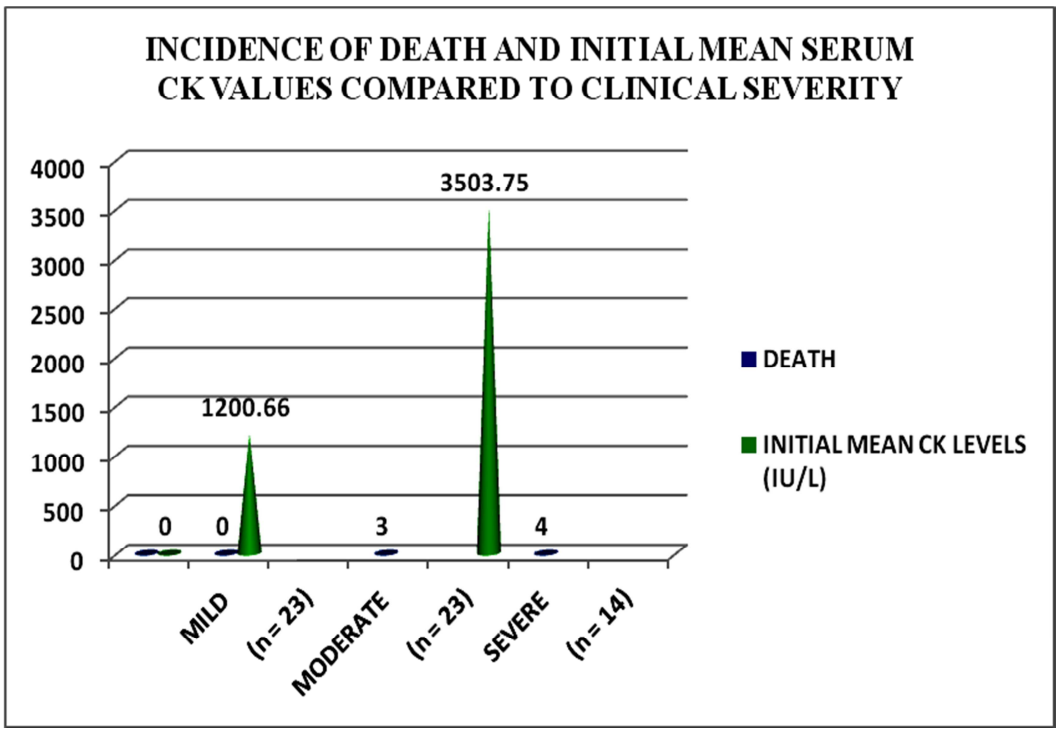


Table 35 : INCIDENCE OF DEATH AND INITIAL MAGNESIUM VALUES COMPARED TO CLINICAL SEVERITY

CLINICAL SEVERITY	DEATH (No.of patients)	INITIAL MEAN MAGNESIUM LEVELS (mg/dl)	P value
MILD (n = 23)	0	0	0.024
MODERATE (n = 23)	03	1.62	
SEVERE (n = 14)	04	1.56	

The incidence of death is more in moderate and severe poisoning who had the initial low serum magnesium levels and it carries significance. (p = 0.024).

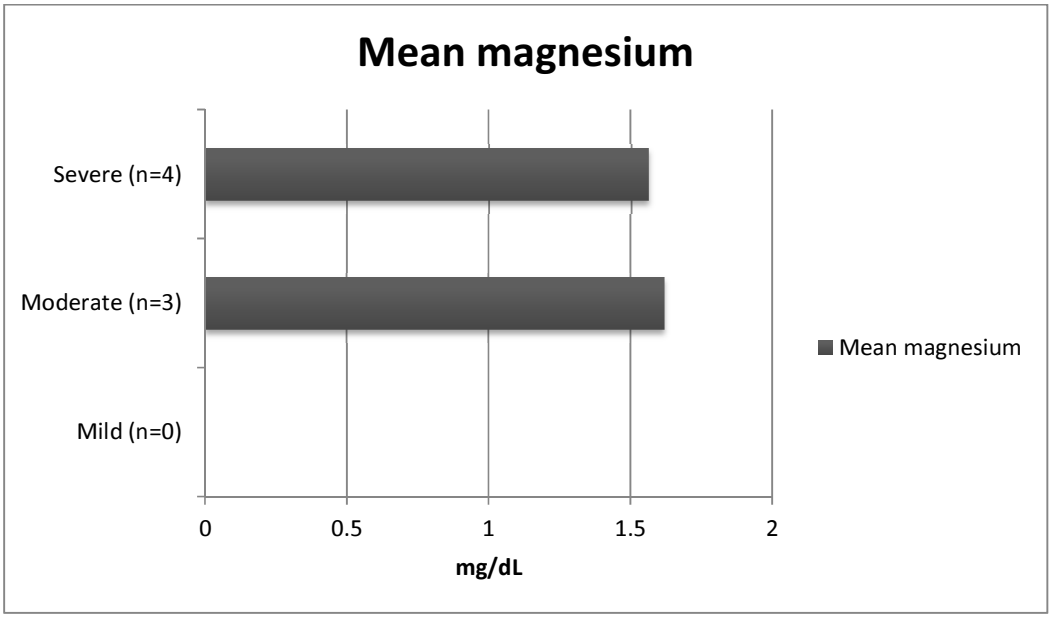
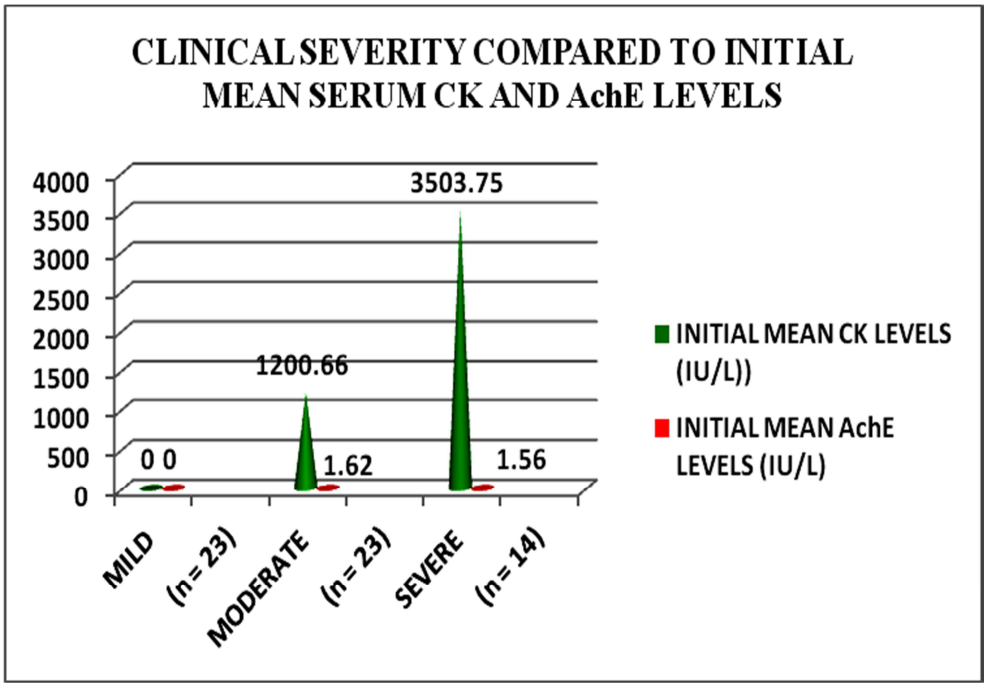


Table 36 :CLINICAL SEVERITY COMPARED TO INITIAL MEAN SERUM CK AND AchE LEVELS

CLINICAL SEVERITY	INITIAL MEAN CK LEVELS (IU/L))	P value	INITIAL MEAN AchE LEVELS (IU/L)	P value
MILD (n = 23)	0	<0.001	0	0.002
MODERATE (n = 23)	1200.66		1.62	
SEVERE (n = 14)	3503.75		1.56	

Clinical severity has positive correlation with the initial serum creatine kinase (p <0.001) and negative correlation with initial serum acetylcholinesterase levels (p = 0.002).



DISCUSSION

Epidemiology of Organophosphorus poisoining

In this series, the organophosphorus poisoning was most prevalent in the age group 21 – 30 years. 49 cases out of 60 were below the age of 40 years. Pyar Ali et al observed the mean age group of 28.6 ±9.8 years from Karachi. Another study from Karachi by Aftab Turab et al observed the age group of 15 – 20 years (44.77%) as predominant. Murat Sungur et al from Turkey observed the mean age group as 30 ±15 years. Karalliedde L., Senanayake N. et al of Srilanka documented 91% of their cases were under the age of 30. Malik et al from Kashmir, revealed the predominant population affected by OPC exposure were under the age of 25. In Mangalore, Karnataka, India, the most common age group to be affected was between 20 – 30 (36.6%). Kuntal Battacharyya et al of Kolkata reported the mean age of 25.5 years. This young age group affected by exposure and also in terms of procurement and productivity. This study throw light on the target age group by improving the management protocol and decreasing the mortality.

In our series, females (n=31) dominated the study population. Probably many male patients were excluded from study due to the mixed poison with alcohol. Malik et al observation of 122 cases in Kashmir valley (females n=114, males n=50), female intoxication was more. In Mangalore and Srilanka had pattern to the case series with male predominance. S.Shivakumar and K.Raghavan et al of Tamilnadu reported 165 cases of organophosphorus

poisoning and sex distribution was with male predominance. Kuntal Battacharya et al from Kolkata showed male predominance. In Southern part of India, males are actively involved in spraying fertilizers and pesticides.

In our case series, 23 out of 60 (38.3%) were agriculturists. Non agriculturist were exposed more to organophosphorus compounds with the suicidal intent. Agriculturist, also accidentally exposed due to the spraying in the field. In Kashmir Valley, two third of the population who had exposed were engaged in apple orchard.

In our series, most of the cases occurred due to ingestion (98.3%) and only one had accidental inhalation (1.7%). The common organophosphorus compounds abused in our series are chlorpyrifos and dimethoate. Kuntal Bhattacharyya et al also described the most frequent compound as Chlorpyrifos (38.1%).

Clinical severity by Peradeniya Organophosphorus Poisoning scale

Kuntal Bhattacharyya et al of Kolkata correlated initial serum creatine kinase with the clinical severity by POP scoring and outcome. In our study, POP scoring was much reliable that it correlated clearly with the duration of hospital stay, development of complications, quantum of exposure and initial serum creatine kinase, magnesium values.

Laboratory correlates:

Serum Creatine Kinase

Patients with acure organophosphorus poisoning are usually monitored by using serum acetylcholinesterase levels which are expected to fall. But, this investigation can not be available in every hospital and is also expensive. Hence, we preferred the estimation of serum creatine kinase instead, which is cheaper.

The initial rise of serum creatine kinase in severe acute organophosphorus poisoning is probably due to the presence of muscle fiber necrosis. This has been demonstrated in two patients by Kuntal Bhattacharyya et al. This occurred even before the development of intermediate syndrome in which CK level is expected to rise. The mean half life of CK is about 1.5 days. With the good management, CK levels may be reduced to normal within 5 days if patient does not develop intermediate syndrome.

In our study, raised serum CK levels at admission significantly correlated with the initial clinical severity by POP scoring, increased atropine requirement, duration of hospital stay. It also correlated with the incidence of intermediate syndrome, arrythmias, renal failure, coma, outcome. Thus, with the morbidity and mortality, it had the pattern of negative correlation with the serum cholinesterase levels at admission. Hence, we concluded that initial serum creatine kinase can be used as parameter for assessing the severity and outcome of acute organophosphorus poisoning replacing serum acetylcholinesterase levels.

Serum Magnesium

Hypomagnesemia seems to occur in any critical illness patients according to various studies. Hypomagnesemia in acute organophosphorus poisoning cases might be due to GI losses, vomiting, diarrhoea, prolonged gastric aspiration, etc., Magnesium is one of the omitted electrolyte in any illness. Since, many manifestations of hypomagnesemia overlap with features of organophosphorus poisoning, it may be the contributory factor in severity and outcome.

In our study, decreased serum magnesium levels at admission correlated with poor outcome in the form of increased atropine requirement, duration of hospital stay, incidence of intermediate syndrome, mechanical ventilation, death and not correlated with the incidence of renal failure, seizures and arrythmias.

There are studies regarding the beneficial effects of intravenous magnesium sulfate in the management protocol of organophosphorus poisoning. The mechanism for magensium sulfate is blocking of ligand gated calcium channels, resulting in reduced acetylcholine release from pre-synaptic terminals.

Hence, it is our opinion from the study that initial reduced serum magnesium level will correlate with poor clinical outcome and intravenous magnesium sulfate also corrects hypomagnesemia in addition to the reduction in acetylcholine relase from pre synaptic terminals, thus reducing morbidity and mortality.

CONCLUSION

1. Peradeniya Organophosphorus Poisoning scale is the excellent classification system for categorising the severity of cases with acute organophosphorus poisoning.

2. Serum creatine kinase can be an efficient biomarker as predictor of severity of acute organophosphorus poisoning and be used instead of serum acetylcholinesterase levels considering the cost and non-availability.

3. Serum magnesium can be used as the predictor of severity of acute organophosphorus poisoning and intravenous magnesium sulfate to be considered for correction to reduce the morbidity and mortality.

RECOMMENDATIONS AND AREAS OF FUTURE RESEARCH

1. Research into the cause for hypomagnesemia in organophosphorus poisoning is worth to be considered.

2. The role of intravenous magnesium sulfate in organophosphorus poisoning needs to be studied in our Indian context and to be included in management protocol.

3. The role of oximes is challenged by many studies. Hence, a large high quality RCT comparing the current WHO recommended regimen with placebo is required to assess the value of pralidoxime in acute organophosphorus poisoning.

4. The role of newer management like fresh frozen plasma therapy, organophosphorus hydrolases, Butrylcholinesterase replacement therapy, α2 adrenergic receptor agonist, extra corporeal clearance needs to be studied to improve the survival rates.

SUMMARY

Organophosphorus poisoning is a menace to the human race both as a weapon of mass destruction and a misused pesticide of self-harm. The case fatality rate exceeded 60% in developing countries where there are many pitfalls in treatment protocol and research activities. Hence, we conducted a study with 60 patients for the possible role of serum creatine kinase and magnesium at poison centre, Rajiv Gandhi Government General Hospital, Chennai.

We found that, raised serum creatine kinase and reduced serum magnesium levels in acute organophosphorus poisoning at admission indicates poor outcome and emphasized the future research regarding the beneficial effect of intermediate magnesium sulfate for correcting hypomagnesemia to reduce the morbidity and mortality.

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SERUM CREATINE PHOSPHOKINASE AND MAGNESIUM AS PROGNOSTIC INDICATORS IN ACUTE ORGANOPHOSPHORUS POISONING

Name :
Age/Sex :
IP No :
Patient ID No :

Symptoms			
❑ Vomiting		❑ Palpitations	
❑ Loose stools		❑ Blurring of vision	
❑ Salivation/Lacrimation/Sweating		❑ Seizures	
❑ Dyspnea		❑ Loss of consciousness	
Poisoning		**Past history**	
Compound		❑ DM	
Amount		❑ HT	
Time of consumption		❑ CAD	
❑ Empty stomach		❑ Bronchial Asthma/COPD	
Personal history			
❑ Smoking		❑ Alcoholism	

Peradeniya Organophosphorus Poisoning scale				
Parameters	**0**	**1**	**2**	**Score**
Pupil size	≥2 mm	<2 mm	Pinpoint	
Respiratory rate	<20/min	≥20/min	≥20/min with central cyanosis	
Heart rate	>60/min	41-60/min	<40/min	
Fasciculation	None	Present Generalized / continuous	Both generalized and continuous	
Level of consciousness	Conscious and rationale	Impaired response to verbal commands	No response to verbal commands	
Seizures	Absent	Present	-	
Grade	Mild [0-3]	Moderate [4-7]	Severe [8-11]	

Systemic examination	
CVS	
RS	
Abdomen	
CNS	

INVESTIGATIONS					
RFT	**LFT**				
Glucose (Fasting)		mg/dl	Total bilirubin		mg/dl
Urea		mmol/l	Direct bilirubin		mg/dl
Creatinine		mmol/l	SGOT		U/l
Electrolytes	SGPT				U/l
Na^+		mEq/l	ALP		U/l
K^+		mEq/l	Total protein		g/dl
Mg^{2+}		mEq/l	Albumin		g/dl
CPK		IU/l	**AchE**		IU/l
ECG					
Chest X-ray					

Course									
	D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D14**	**D21**
Atropine requirement									
Mechanical ventilation									
Arrhythmias									
Renal failure									

ஆராய்ச்சிதகவல்தாள்

சென்னைஇராஜிவ்காந்திஅரசுபொதுமருத்துவமனையில்அனுமதிக்கப்படும்பூச்சிக்கொல்லிமருந்தினைஉட்கொண்டநோயாளிகளைப்பற்றியஒருஆராய்ச்சிநடைபெற்றுவருகிறது.

பூச்சிக்கொல்லிமருந்தினைஉட்கொண்டநோயாளிகளின்நச்சுபாதிப்பின் தீவிரத்தைஇரத்தத்தில்ஏற்படும்சிலவேதியியல்மாற்றங்களின்மூலம்அறிவதேஇந்தஆராய்ச்சியின்நோக்கமாகும்.

நீங்களும்இந்தஆராய்ச்சியில்பங்கேற்கநாங்கள்விரும்புகிறோம். முடிவுகளைஅல்லதுகருத்துக்களைவெளியிடும்போதோஅல்லதுஆராய்ச்சியின் போதோதங்களதுபெயரையோஅல்லதுஅடையாளங்களையோவெளியிடமாட்டோம்என்பதையும்தெரிவித்துக்கொள்கிறோம்.

இந்தஆராய்ச்சியில்பங்கேற்பதுதங்களுடையவிருப்பத்தின்பேரில்தான்இருக்கிறது.

மேலும்நீங்கள்எந்நேரமும்இந்தஆராய்ச்சியிலிருத்துபின்வாங்கலாம்என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்தசிறப்புப்பரிசோதனைகளின்முடிவுகளைஆராய்ச்சியின்போதுஅல்லதுஆராய்ச்சியின்முடிவில்தங்களுக்குஅறிவிப்போம்என்பதையும்தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி:

ஆராய்ச்சிஒப்புதல்கடிதம்

ஆராய்ச்சி தலைப்பு:

பூச்சிக் கொல்லி மருந்தினை உட்கொண்ட நோயாளிகளின் நச்சு பாதிப்பின் தீவிரத்தை இரத்தத்தில் ஏற்படும் சில வேதியியல் மாற்றங்களின் மூலம் அறிவது பற்றிய ஆராய்ச்சி.

பெயர்:	தேதி:
வயது:	உள்நோயாளி எண்:
பால்:	ஆராய்ச்சி சேர்க்கை எண்:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது. எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறேன்.

பூச்சிக் கொல்லி மருந்து உட்கொள்வதால் ஏற்படும் பாதிப்புகள் குறித்தும், அதன் தீவிரத்தைக் கண்டறிய மேற்கொள்ளப்படும் பரிசோதனைகள் குறித்தும் ஆராய்ச்சியாளர் கூற முழுவதும் விளங்கப்பெற்றேன்.

மேற்கொண்ட பரிசோதனையின் போது ஏற்படக்கூடிய பின்விளைவுகளையும் முழுவதும் உணர்ந்து இந்த பரிசோதனைக்கு மனமார சம்மதிக்கிறேன்.

கையொப்பம்

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. R. Subrmanian
PG in MD General Medicine
Madras Medical College, Chennai -3

Dear Dr. R. Subrmanian

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Serum Creatine kinase and magnesium as prognostic indicators in acute organophosphorus poisoning " No.18062012.

The following members of Ethics Committee were present in the meeting held on 19.06.2012 conducted at Madras Medical College, Chennai -3.

1.	Dr. S.K. Rajan. M.D.,FRCP.,DSc	-- Chairperson
2.	Prof. K. Ramadevi MD Prof of Biochemistry, MMC, Ch-3	-- Member
3.	Prof. R. Nandhini MD Director, Inst. of Pharmacology ,MMC, Ch-3	-- Member
4.	Prof. C. Rajendiran, MD Director , Inst. of Internal Medicine, MMC, Ch-3	-- Member
5.	Prof. S. Deivanayagam MS Prof of Surgery, MMC, Ch-3	-- Member
6.	Prof. A. Radhakrishnan MD Prof of Internal Medicine, MMC, Ch-3	-- Member

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

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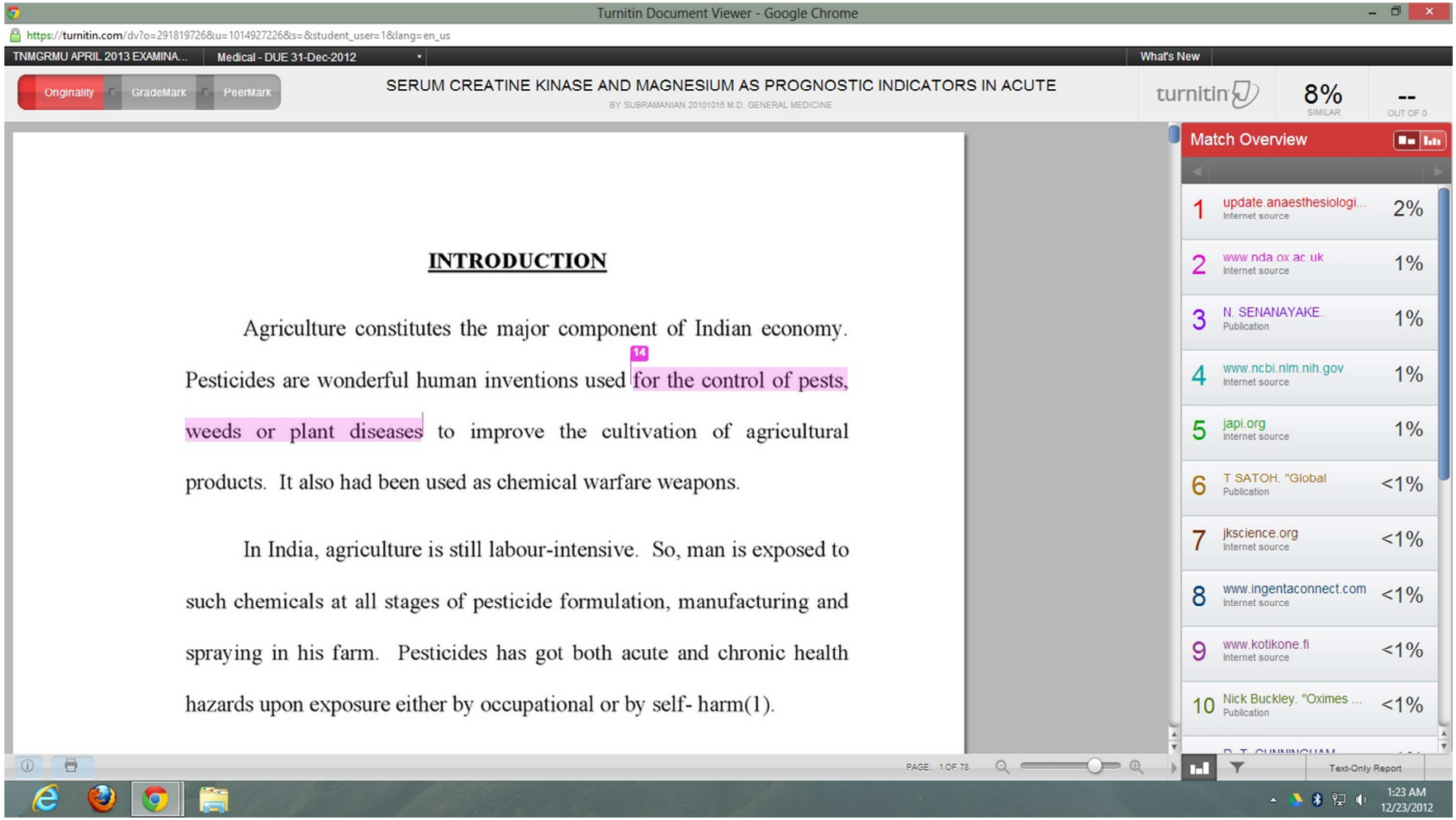
INTRODUCTION Agriculture constitutes the major component of Indian economy. Pesticides are wonderful human inventions used for the control of pests, weeds or plant diseases to improve the cultivation of agricultural products. It also had been used as chemical warfare weapons. In India, agriculture is still labour-intensive. So, man is exposed to such chemicals at all stages of pesticide formulation, manufacturing and spraying in his farm. Pesticides has got both acute and chronic health hazards upon exposure either by occupational or by self- harm(1). Poisoning constitutes about 60% of self-harm(1) in rural Asia. Organophosphate compounds account for 80% of pesticide poisoning. Ravi et al...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INTRODUCTION
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In India, agriculture is still labour-intensive. So, man is exposed to such chemicals at all stages of pesticide formulation, manufacturing and spraying in his farm. Pesticides has got both acute and chronic health hazards upon exposure either by occupational or by self- harm(1).
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MASTER CHART

ID	Age	Sex	Occupation	Poison	Route	Quantity	Duration of symptoms	POP score	RFT1	RFT2	Sodium	Potassium	pH	Calcium
1	42	M	Agri	Triazophos	ING	20	10	MILD	NORMAL	NORMAL	137	3.5	7.37	9.8
2	21	F	Non-Agri	chlorpyrifos	ING	50	4	MILD	NORMAL	NORMAL	142	3.9	7.34	9.8
3	23	F	Non-Agri	chlorpyrifos	ING	80	5	SEVERE	NORMAL	NORMAL	142	3.1	7.3	8.6
4	45	M	Agri	Temephos	ING	45	8	MILD	NORMAL	NORMAL	151	4.2	7.38	8.9
5	21	F	Non-Agri	Monochrotophos	ING	30	4	MODERATE	NORMAL	NORMAL	134	3.9	7.36	8.8
6	35	F	Non-Agri	Triazophos	ING	45	4	MILD	NORMAL	NORMAL	143	4.2	7.35	10.2
7	18	F	Non-Agri	Dimethoate	ING	70	3	MODERATE	NORMAL	NORMAL	133	3.2	7.34	9.4
8	24	F	Non-Agri	Monochrotophos	ING	120	6	MODERATE	NORMAL	NORMAL	137	4.3	7.42	10.1
9	55	M	Agri	Prophenophos	ING	100	6	MODERATE	NORMAL	NORMAL	145	3.5	7.44	8.6
10	34	F	Agri	Triazophos	ING	150	5	SEVERE	NORMAL	ABN	136	3.9	7.36	9.3
11	28	M	Agri	Triazophos	ING	60	5	MILD	NORMAL	NORMAL	136	4.3	7.43	8.9
12	25	M	Non-Agri	Monochrotophos	ING	20	7	MODERATE	NORMAL	ABN	142	4.1	7.42	8.7
13	55	M	Agri	Dichlorovas	ING	100	11	MODERATE	NORMAL	ABN	130	4.3	7.2	8.6
14	19	M	Non-Agri	chlorpyrifos	ING	60	6	SEVERE	NORMAL	NORMAL	143	4.1	7.42	9.8
15	32	M	Non-Agri	Diazinon	ING	70	4	SEVERE	NORMAL	NORMAL	136	4	7.33	9

16	34	F	Agri	Prophenophos	ING	70	6	MILD	NORMAL	NORMAL	143	4.3	7.45	9.3
17	26	F	Non-Agri	Prophenophos	ING	15	8	MILD	NORMAL	NORMAL	144	4.7	7.4	8.9
18	27	M	Agri	chlorpyrifos	ING	30	7	MODERATE	NORMAL	ABN	126	4.8	7.41	8.9
19	18	F	Non-Agri	Temephos	ING	60	4	MODERATE	NORMAL	ABN	132	5.2	7.32	8.6
20	16	M	Non-Agri	chlorpyrifos	ING	100	5	SEVERE	NORMAL	NORMAL	136	4.2	7.43	8.7
21	51	M	Agri	Dimethoate	ING	100	6	MILD	NORMAL	NORMAL	142	4.4	7.36	8.6
22	24	M	Non-Agri	Dimethoate	ING	40	9	MILD	NORMAL	NORMAL	136	3.9	7.38	8.6
23	51	M	Agri	Temephos	ING	40	3	SEVERE	NORMAL	ABN	135	4.6	7.32	7.3
24	18	F	Non-Agri	Prophenophos	ING	20	4	MILD	NORMAL	NORMAL	143	3.8	7.39	8.9
25	26	M	Agri	Dimethoate	ING	150	7	MODERATE	NORMAL	NORMAL	135	3.7	7.32	9.8
26	21	M	Agri	Prophenophos	ING	70	3	SEVERE	NORMAL	ABN	135	3.8	7.43	8.9
27	32	F	Non-Agri	Monochrotophos	ING	60	5	SEVERE	NORMAL	NORMAL	130	3.1	7.3	9.2
28	34	F	Non-Agri	Temephos	ING	50	4	MILD	NORMAL	NORMAL	145	3.6	7.36	8.9
29	25	F	Non-Agri	chlorpyrifos	ING	30	4	MODERATE	NORMAL	NORMAL	138	3.8	7.4	8.7
30	38	F	Non-Agri	Dimethoate	ING	50	8	MILD	NORMAL	NORMAL	152	4.2	7.35	9.5
31	31	M	Agri	Temephos	ING	40	5	MILD	NORMAL	NORMAL	142	3.8	7.36	9.7
32	29	M	Agri	Monochrotophos	ING	60	9	MODERATE	NORMAL	ABN	134	4.2	7.33	9.8
33	37	F	Agri	Triazophos	ING	50	5	SEVERE	NORMAL	NORMAL	138	3.4	7.34	8.6
34	28	M	Non-Agri	Chlorpyrifos	ING	50	8	MODERATE	NORMAL	NORMAL	134	4.2	7.42	8.9
35	24	M	Agri	chlorpyrifos	ING	20	3	MODERATE	NORMAL	ABN	143	3.6	7.35	9.4
36	26	F	Non-Agri	Monochrotophos	ING	50	3	SEVERE	NORMAL	NORMAL	123	5.1	7.23	8.9
37	41	F	Agri	Quinalphos	ING	100	6	MODERATE	NORMAL	NORMAL	145	3.9	7.4	9.6

38	17	M	Non-Agri	Prophenophos	ING	30	3	MILD	NORMAL	NORMAL	143	3.8	7.43	8.7
39	18	F	Non-Agri	chlorpyrifos	ING	40	6	MILD	NORMAL	NORMAL	144	4.3	7.4	8.7
40	42	M	Agri	Dimethoate	INH		6	MILD	NORMAL	NORMAL	145	4.5	7.45	9.2
41	36	M	Agri	Monochrotophos	ING	60	8	MODERATE	NORMAL	ABN	143	3.8	7.38	10.4
42	34	M	Non-Agri	chlorpyrifos	ING	50	6	MILD	NORMAL	NORMAL	136	3.6	7.43	10.2
43	34	M	Agri	Prophenophos	ING	100	4	MODERATE	NORMAL	NORMAL	143	3.8	7.42	8.9
44	33	M	Agri	Prophenophos	ING	50	6	MODERATE	NORMAL	ABN	145	4.1	7.36	8.8
45	19	F	Non-Agri	Dimethoate	ING	20	5	MILD	NORMAL	NORMAL	142	4.4	7.42	9.8
46	24	F	Non-Agri	Monochrotophos	ING	60	3	SEVERE	NORMAL	NORMAL	139	3.2	7.4	9.2
47	31	M	Non-Agri	chlorpyrifos	ING	100	5	MODERATE	NORMAL	NORMAL	135	4.5	7.36	8.8
48	23	F	Non-Agri	chlorpyrifos	ING	120	5	SEVERE	NORMAL	NORMAL	125	4.9	7.31	8.7
49	27	F	Non-Agri	Triazophos	ING	30	4	MILD	NORMAL	NORMAL	142	4.5	7.4	9.5
50	45	M	Non-Agri	Chlorpyrifos	ING	100	4	MILD	NORMAL	NORMAL	137	4.4	7.41	10.8
51	35	F	Non-Agri	Dimethoate	ING	70	8	MODERATE	NORMAL	NORMAL	129	3.8	7.36	9.6
52	19	F	Non-Agri	Triazophos	ING	30	5	MILD	NORMAL	NORMAL	136	4.2	7.43	9.6
53	15	F	Non-Agri	Temephos	ING	50	5	MODERATE	NORMAL	NORMAL	145	3.8	7.4	9.8
54	26	F	Non-Agri	chlorpyrifos	ING	40	5	MILD	NORMAL	NORMAL	151	4.2	7.43	9.8
55	28	M	Agri	Dimethoate	ING	35	7	MILD	NORMAL	NORMAL	143	4.4	7.32	9.2
56	33	M	Agri	Triazophos	ING	100	6	MODERATE	NORMAL	NORMAL	146	2	7.43	8.3
57	24	F	Non-Agri	chlorpyrifos	ING	150	3	SEVERE	NORMAL	ABN	134	3.4	7.2	6.8
58	43	F	Non-Agri	Dimethoate	ING	50	5	MODERATE	NORMAL	NORMAL	139	3.5	7.36	8.8
59	43	F	Non-Agri	Monochrotophos	ING	60	3	SEVERE	NORMAL	ABN	137	3.8	7.43	9.5

60	17	F	Non-Agri	chlorpyrifos	ING	60	5	MODERATE	NORMAL	NORMAL	152	3.4	7.3	9.2

ID	Age	Sex	Magnesium	AChE	CK	Arrhythmia	Intermediate syndrome	AtropineDose	Ventilator	Ventilation duration	Seizures	Coma	Stay	Outcome
1	42	M	1.9	3300	140	A	A	6	N		N	N	4	Discharge
2	21	F	2.1	2800	110	A	A	6	N		N	N	5	Discharge
3	23	F	1.33	1320	8200	A	A	52	Y	20	N	Y	32	Death
4	45	M	1.9	1467	145	A	A	10	N		N	N	6	Discharge
5	21	F	1.7	1790	230	A	A	32	N		N	N	11	Discharge
6	35	F	1.7	1300	70	A	A	11	N		N	N	7	Discharge
7	18	F	1.5	2390	560	A	A	23	Y	7	N	N	20	Death
8	24	F	1.6	1370	130	A	A	21	Y	8	N	N	16	Discharge
9	55	M	1.7	2300	1700	A	P	23	Y	6	N	N	15	Death
10	34	F	1.6	790	1480	P	A	13	Y	6	N	N	18	Death
11	28	M	1.8	3200	135	A	A	4	N		N	N	6	Discharge
12	25	M	1.7	2130	560	A	P	24	N		N	N	12	Discharge
13	55	M	1.7	2120	210	A	A	10	N		N	N	7	Discharge

14	19	M	1.6	1320	2300	A	A	23	N		N	N	12	Discharge
15	32	M	1.4	1423	512	A	P	42	Y	8	N	N	15	Discharge
16	34	F	1.9	3300	165	A	A	9	N		N	N	6	Discharge
17	26	F	2.1	3290	130	A	A	12	N		N	N	7	Discharge
18	27	M	1.6	2430	780	A	A	23	Y	4	N	N	17	Discharge
19	18	F	1.6	1690	580	A	A	24	Y	4	N	N	12	Discharge
20	16	M	1.7	1200	870	A	A	21	Y	8	N	Y	31	Death
21	51	M	1.6	2100	135	A	P	9	N		N	N	4	Discharge
22	24	M	1.86	2434	211	A	A	12	N		N	N	7	Discharge
23	51	M	1.5	980	5400	A	A	34	Y	16	N	N	23	Discharge
24	18	F	2.2	2800	110	A	A	4	N		N	N	4	Discharge
25	26	M	1.5	1980	1320	P	A	32	Y	10	N	N	23	Discharge
26	21	M	1.6	1320	2300	A	A	32	Y	7	N	N	18	Discharge
27	32	F	1.5	980	2300	A	P	35	Y	7	N	N	22	Discharge
28	34	F	2.3	2670	152	A	A	12	N		N	N	7	Discharge
29	25	F	1.5	2300	320	A	A	12	N		N	N	6	Discharge
30	38	F	1.9	2700	160	A	A	6	N		N	N	5	Discharge
31	31	M	1.9	1900	215	A	A	12	N		N	N	6	Discharge
32	29	M	1.6	2100	890	A	A	24	Y	7	N	N	14	Discharge
33	37	F	1.7	870	580	A	P	31	Y	6	N	N	15	Discharge
34	28	M	1.8	4012	910	A	A	21	N		N	N	6	Discharge
35	24	M	1.6	1420	460	A	A	21	N		N	N	12	Discharge

36	26	F	1.7	1230	790	A	A	21	Y	8	N	N	20	Discharge
37	41	F	1.66	2013	280	A	P	23	N		N	N	6	Discharge
38	17	M	1.8	1900	220	A	A	12	N		N	N	6	Discharge
39	18	F	1.9	3190	127	A	A	8	N		N	N	5	Discharge
40	42	M	1.9	3100	165	A	A	3	N		N	N	4	Discharge
41	36	M	1.8	2130	560	A	A	31	Y	5	N	N	9	Discharge
42	34	M	1.72	1300	126	A	A	12	N		N	N	5	Discharge
43	34	M	1.7	1245	365	A	A	21	Y	5	N	N	12	Discharge
44	33	M	1.8	1560	170	A	P	18	Y	5	N	N	13	Discharge
45	19	F	1.72	2398	164	A	A	12	N		N	N	5	Discharge
46	24	F	1.4	1100	5300	A	P	45	Y	13	N	Y	27	Discharge
47	31	M	1.9	1230	320	A	A	31	Y	4	N	N	13	Discharge
48	23	F	1.6	560	2300	A	A	23	Y	6	N	N	13	Discharge
49	27	F	1.8	3010	90	A	A	8	N		N	N	5	Discharge
50	45	M	1.9	1278	162	A	A	21	Y	7	N	N	16	Discharge
51	35	F	1.6	2530	800	A	A	34	Y	6	N	N	16	Discharge
52	19	F	2.1	3300	140	A	A	5	N		N	N	4	Discharge
53	15	F	1.66	2149	1342	A	A	24	Y	8	N	N	23	Death
54	26	F	1.9	3100	165	A	A	5	N		N	N	5	Discharge
55	28	M	2	2870	145	A	A	9	N		N	N	6	Discharge
56	33	M	1.41	1410	148	A	A	19	N		N	N	5	Discharge
57	24	F	1.6	790	3465	P	A	32	Y	13	N	N	23	Death

58	43	F	1.7	2200	520	A	A	18	Y	4	N	N	13	Discharge
59	43	F	1.5	1200	8600	A	A	42	Y	12	N	N	23	Discharge
60	17	F	1.5	1560	810	A	P	20	N		Y	N	12	Discharge